UNITED STATES DISTRICT COURT
DISTRICT OF DELAWARE

Cephalon, Inc. et al., Plaintiffs v. Mylan Pharmaceuticals Inc. et al., Defendants.	Civil Action No. 11-0164-SLR

MYLAN DEFENDANTS' PROPOSED FINDINGS OF FACT AND CONCLUSIONS OF LAW ON THE INVALIDITY OF U.S. PATENTS 8,092,832 AND 8,119,158

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INTRODUCTION

Just before trial, plaintiffs, Cephalon, Inc. and CIMA Labs., Inc. (collectively, "Cephalon"), narrowed the patents and claims being asserted against Defendants, Mylan Pharmaceuticals, Inc. and Mylan, Inc. (collectively "Mylan"), to four patents and a total of seventeen claims. Two of those patents, U.S. patents 8,092,832 and 8,119,158 (the "'832 patent" and "'158 patent," respectively), are related patents with the same specification and priority date. Dr. Derek Moe is the first named inventor on both the '832 and '158 patents, so those patents were sometimes referred to at trial as the "Moe patents." The evidence presented at trial established that all of the asserted claims of the '832 and '158 patents are invalid. Pursuant to the Court's post-trial briefing schedule, Mylan hereby submits its proposed findings of fact and conclusions of law with respect to the invalidity of the asserted claims of the '832 and '158 patents. The non-infringement defenses as to the '158 patent and U.S. patents 6,200,604 (the "'604 patent") and 6,974,590 (the "'590 patent") will be addressed in Mylan's responsive post-trial brief.

A. The Asserted Claims of the '832 and '158 Patents Are Invalid

By listing the '832 and '158 patents in the FDA's Orange Book and asserting them against Mylan and other companies, Cephalon seeks to extend the patent life for its Fentora® product and thereby delay generic competition by up to nine years beyond the expiration of its '604 and '590 patents. Cephalon is not entitled to any additional patent protection, because the asserted claims of the '832 and '158 patents are invalid. The only alleged novelty of those claims over the disclosure of the prior art '604 patent is:

- The recitation of specific numerical dosages or dosage ranges that were already well known to be pharmaceutically effective and were widely used for transmucosal administration of fentanyl for precisely the same uses.

- The use of mannitol as the tablet filler, even though it was one of five fillers listed by name in the '604 patent and even though it was indisputably one of the most commonly used fillers, especially for tablets intended to be held in the mouth.
- The use of starch glycolate as a disintegrant, even though it was described in the '604 patent as a suitable disintegrant by its synonym, modified potato starch, and even though it was one of the most commonly used disintegrants and one of the only three so-called "superdisintegrants" available at the time for use in tablet formulations.

These features were not novel. They had already been disclosed in the '604 patent, and there is no dispute that each and every other feature claimed in the '832 and '158 patents was described in the '604 patent. As proven at trial and explained in detail herein, the asserted claims are invalid under 35 U.S.C. § 102(b) and § 103 as both anticipated and obvious.

i. The Asserted Claims of the '832 and '158 Patents Were Anticipated by the '604 Patent

The '604 patent, entitled "Sublingual Buccal Effervescent," is not only one of the patents that is being asserted by Cephalon in this case, but it also discloses all of the elements of the asserted claims of the '832 and '158 patents. There was no dispute at trial that the '604 patent, which issued more than a year before the claimed priority date for the '832 and '158 patents, is the closest prior art to the asserted claims of both the '832 and '158 patents. The '604 patent claims and describes, *inter alia*, the use of effervescent agents in combination with a pH adjusting substance to deliver drugs including fentanyl through the oral mucosa. Example 1 of the '604 patent describes in detail a particular formulation for a 1000 mcg fentanyl effervescent tablet, including pH adjustment, for delivery through the oral mucosa. The specification of the '604 patent describes the use of standard types of pharmaceutical excipients, such as fillers,

disintegrants, and flavorings and identifies suitable ingredients in each category for use in the formulations described therein.

While conceding that the '604 patent discloses effervescent tablets with pH adjustment for delivering fentanyl through the oral mucosa, Cephalon asserts that three elements of the asserted claims are not anticipated by the disclosure of the '604 patent:

(1) the specific dosages of fentanyl claimed;

(2) use of the filler mannitol in the claimed amounts; and

(3) use of the disintegrant sodium starch glycolate in the claimed amounts.

The evidence at trial was overwhelming that when the disclosures of the '604 patent are read through the eyes of the person of ordinary skill in the art -- as the governing law requires -- these three elements are all disclosed by the '604 patent.

First, the '604 patent teaches the use of "a pharmaceutically effective amount" of the orally administrable medicament in its invention, and teaches that fentanyl is such an orally administrable medicament. Example 1 of the '604 patent describes a formulation using fentanyl at a dosage only slightly above the claimed range (1000 mcg vs. about 800 mcg) as the orally administrable medicament. Fentanyl is one of only two medicaments used in the examples of the '604 patent. The testimony at trial was undisputed that the claimed ranges of fentanyl dosages in the '832 and '158 patents are pharmaceutically effective amounts of fentanyl and that the person of ordinary skill in the art would have been aware of that fact. Indeed, Dr. Moe himself testified that the dosages used by Cephalon were based on, *inter alia,* the commercially available fentanyl product Actiq®, which was available at those same dosages. Because Mylan has shown by clear and convincing evidence that the person of ordinary skill in the art readily would have understood the '604 patent's disclosure of a pharmaceutically effective amount of fentanyl to

include dosages in the claimed range, the ’604 patent discloses this element of the asserted claims.

Second, the ‘604 patent identifies mannitol as the first suitable filler listed in a group of only five such fillers. In addition, the ‘604 patent uses mannitol as the filler in amounts within the claimed ranges as the filler in one of the two examples of the ‘604 patent. Moreover, Cephalon’s witnesses concede that there is nothing in the ‘604 patent teaching away from the selection of mannitol as the filler in the formulation and that the claimed ranges for amounts of mannitol are completely typical in the art. Because the ‘604 patent’s disclosure of mannitol as a suitable filler would allow the person of ordinary skill in the art readily to envision using mannitol in the claimed amounts as the filler in the formulations taught therein, this element of the asserted claims is also disclosed by the ‘604 patent.

Third, the ‘604 patent describes the use of a starch glycolate, specifically sodium starch glycolate, by identifying it as one of the non-effervescent disintegrants suitable for use in the effervescent formulations for delivery of drug through the oral mucosa. The disintegrants described in the ‘604 patent are often described using multiple names. For example, one of the disintegrants is described as crospovidone in the specification’s list of suitable disintegrants but as “polyvinylphrrolidone [sic, polyvinylpyrrolidone], cross-linked” when used in Example 1. Likewise, the list of suitable disintegrants in the ‘604 patent does not use the words “starch glycolate” in describing the non-effervescent disintegrants suitable for use in the formulations. Instead, the specification refers to the use of modified potato starches in the list of suitable non-effervescent disintegrants. This difference in terminology does not diminish the anticipatory effect of this disclosure in the ‘604 patent. The testimony at trial establishes beyond legitimate dispute that the person of ordinary skill in the art would have understood the ‘604 patent’s

description of modified potato starch as a suitable disintegrant to be a reference to sodium starch glycolate. There was no dispute at trial that sodium starch glycolate was the only modified potato starch disintegrant, and that it was one of only three superdisintegrants, used in pharmaceutical formulations. The '604 patent used crospovidone, one of the other superdisintegrants in Example 1. Because Mylan has shown by clear and convincing evidence that the person of ordinary skill would have understood the disclosure of the '604 patent to teach the use of sodium starch glycolate as the disintegrant in the fentanyl buccal tablet formulation, this element is disclosed by the '604 patent.

Because the '604 patent, when properly read and evaluated from the viewpoint of the person of ordinary skill in the art, discloses each element of the asserted claims of the '832 and '158 patent, those claims are invalid as anticipated.

B. The Asserted Claims of the '832 and '158 Patents are Invalid as Obvious

Given the disclosures of the '604 patent, as described above, there is no substantial dispute that the asserted claims of the '832 and '158 patents would have been obvious in light of the '604 patent. The evidence at trial established that the dosages of fentanyl claimed in the '832 and '158 patents are no different than the dosages used in the prior art, commercially available Actiq® product -- a product that was well known to persons working in this field. Likewise, even Cephalon's witnesses did not dispute that (1) mannitol was described as one of five suitable fillers in the '604 patent and (2) that mannitol was commonly used, particularly in products that are held in the mouth rather than immediately swallowed. Finally, it was established in the testimony at trial that the person of ordinary skill would have known that sodium starch glycolate was one of only three superdisintegrants and the person of ordinary skill in the art would have understood that it could be readily substituted for the other superdisintegrant used in Example 1 of the '604 patent for a short disintegration time formulation.

Cephalon's primary effort to overcome the obviousness case established at trial, as it was in the Patent Office, was to argue that the formulation containing mannitol as the filler and sodium starch glycolate as the disintegrant provides an unexpected benefit of higher blood levels of fentanyl. At trial, the parties' experts disagreed as to whether or not the data on which Cephalon relies was sufficient to show that any unexpected benefit of the claimed formulations exists. As discussed below, the evidence at trial did not support the conclusion that the claimed formulations possess any unexpected benefits.

This Court need not even resolve that dispute between the experts, however, because the undisputed facts demonstrate that Cephalon's evidence of unexpected benefits is insufficient as a matter of law to support the validity of the asserted claims. It is well-established that, to be relevant to the obviousness inquiry, unexpected benefits must be shown to be commensurate with the scope of the claims, *i.e.*, there must be evidence that those unexpected benefits are achieved not just at one point within the claimed range but across the entire claimed range. There is no dispute that the only data alleged to show unexpected benefits is for a specific formulation using only one amount of fentanyl, one amount of mannitol and one amount of sodium starch glycolate. The asserted patent claims cover broad ranges for each of these elements, and Cephalon produced no evidence that the alleged unexpected benefits occur across the claimed ranges. Indeed, Cephalon's witnesses had to admit that there is no evidence as to even whether the alleged unexpected benefits are attributable to the use of mannitol, the use of sodium starch glycolate, or some combination of the two. Even if Cephalon had demonstrated unexpected benefits for the single formulation that it tested, those results are not commensurate with the broad scope of the asserted patent claims and therefore cannot overcome the obviousness showing. As discussed *infra*, Cephalon's other asserted objective indicia of non-

obviousness also fail to provide any basis to overcome the strong showing of obviousness made by Mylan.

Because Mylan has shown by clear and convincing evidence that the differences between the subject matter of the asserted claims of the ‘832 and ‘158 patents and the prior art is such that it would have been obvious to the person of ordinary skill in the art, those claims are invalid under 35 U.S.C. § 103.

DEFENDANTS' PROPOSED FINDINGS OF FACT

I. BACKGROUND

A. The Patents-In-Suit

i. History and Prosecution of the '832 and '158 patents

1. The '832 and '158 patents are related applications that claim priority to the same provisional patent application. JTX 6 at 2; JTX 8 at 2. The two patents have the same three inventors: Dr. Derek Moe, Dr. Vikas Agarwal and Dr. Wahlid Habib, all of CIMA. *Id*. CIMA was subsequently purchased by Plaintiff Cephalon. D.I. 138 at ¶¶ 30, 34.

2. The applications that led to the issuance of the '832 patent and the '158 patent were filed on November 29, 2010. JTX 6 at 2; JTX 8 at 2. The '832 and '158 patents claim priority to, at the earliest, a provisional application filed on December 31, 2003. *Id*.

3. The '832 patent is entitled "Generally Linear Effervescent Oral Fentanyl Dosage Form and Methods of Administration." JTX 8 at 2. The '158 patent is entitled "Effervescent Oral Fentanyl Dosage Form and Methods of Administering Fentanyl." JTX 6 at 2.

4. The specifications of the '832 and '158 patents make multiple references to the improvement of the alleged invention over the commercial Actiq® product. *See, e.g.*, JTX 8, col. 2, l. 58-col. 3, l. 17; col. 6, ll. 40-53. The first named inventor, Dr. Moe, confirmed that statements made in the specifications concerning the alleged benefits of the invention were based on comparing the claimed invention to the Actiq® product, not the '604 patent. D.I. 148 at 292:25-294:12. Cephalon's expert Dr. Illum also conceded that many of the advantages discussed in the specifications of the '832 and '158 patents referred to advantages over the Actiq® product. D.I. 151 at 1216:11-19. Dr. Blinderman, Cephalon's pain treatment expert, identified certain disadvantages of the Actiq® product that were resolved by Fentora®, but

admitted that the invention of the prior art '604 patent would not have those disadvantages of Actiq®. D.I. 147 at 113:5-114:24.

5. Inventor Moe agreed that the lactose/crospovidone formulation (*i.e.*, Example 1 of the '604 patent) is more closely related to the Fentora® product than to the Actiq® product. D.I. 148 at 292:17-21.

6. During prosecution of the patents-in-suit and the related patents, Cephalon overcame obviousness rejections by submitting multiple declarations from Dr. Moe concerning asserted unexpected benefits of the claimed formulations. *See* PTX 29; PTX 132. In those declarations, Dr. Moe provided data from two pharmacokinetic studies that measured the blood levels obtained from administration of fentanyl effervescent buccal tablets with lactose as a filler and crospovidone as a disintegrant (the "lactose/crospovidone formulation") and two other studies that measured the blood levels obtained from administration of fentanyl effervescent buccal tablets with mannitol as a filler and sodium starch glycolate as a disintegrant (the "mannitol/sodium starch glycolate formulation"). *Id.*; D.I. 148 at 298:11-299:13.

7. Cephalon has never conducted any studies to compare the blood levels obtained from the lactose/crospovidone formulation and the mannitol/sodium starch glycolate formulation head-to-head in the same study. D.I. 148 at 299:14-19. Therefore, all the comparisons of the two formulations that Dr. Moe made were based on indirect comparisons of data from two different studies. D.I. 148 at 299:14-300:3.

8. Dr. Moe did not perform any statistical analysis on the data that he submitted to the Patent Office and described as providing evidence to support the claim of unexpected benefits. D.I. 148 at 302:23-303:6; 309:11-16. Dr. Moe made claims of unexpected benefits based on three sets of data: (1) comparing the results for the 270 mcg dose of the

lactose/crospovidone formulation in the 99-09 study with the results for the 270 mcg dose of the mannitol/sodium starch glycolate formulation in the 99-11 study; (2) comparing the results for the 810 mcg dose of the lactose/crospovidone formulation in the 99-10 study with the results for the 810 mcg dose of the mannitol/sodium starch glycolate formulation in the 99-11 study; and (3) comparing the results for the 810 mcg dose of the lactose/crospovidone formulation in the 99-10 study with the results for the 810 mcg dose of the mannitol/sodium starch glycolate formulation in the 99-18 study. PTX 132 at 7.

9. Dr. Moe testified that at the time that he made his declarations to the Patent Office that he believed that it was valid to make these three comparisons to evaluate the relative performance of the two formulations. D.I. 148 at 302:11-16; 310:3-16.

10. In Cephalon's own internal documents, the chart prepared by its outside pharmacokinetic consultants showed that for all four fentanyl dosages tested (including the 810 mcg dosage) in the 99-09; 99-10 and 99-11 studies showed an overlap in the error bars. PTX 131 at 3; D.I. 148 at 312:8-313:12.

11. None of the comparisons made by Dr. Moe in his declarations to the Patent Office show a statistically significant difference between the mean blood levels at the 0.01 confidence level. D.I. 150 at 1039:6-18; 1041:10-25. Two of the three comparisons made by Dr. Moe in his declarations (the comparison of the 270 mcg doses and the comparison of the 810 mcg doses in the 99-10 and 99-18 studies) do not show a statistically significant difference between the mean blood levels even at the less stringent 0.05 confidence level. D.I. 150 at 1043:10-18.

12. Despite Dr. Moe's reliance on all three comparisons before the Patent Office, Cephalon's pharmacokinetics expert, Dr. Markus Jerling, excluded the two comparisons that show no statistically significant difference between the formulations from his analysis of the

unexpected benefits that Cephalon now claims support the validity of the '832 and '158 patents. D.I. 151 at 1169:24-1170:18.

ii. The Asserted Claims of the '832 Patent

13. Cephalon has asserted claims 1, 3, 4, and 5 of the '832 patent against Mylan.

14. Claim 1 of the '832 patent covers an effervescent fentanyl tablet with a particular formulation containing specified ingredients in a range of amounts. JTX 8, col. 36. Claim 1 is the only independent claim of the '832 patent. JTX 8, col. 36.

15. Claim 1 requires that the claimed tablet include "an amount of fentanyl free base or an equivalent amount of salt thereof selected from the group consisting of about 100 micrograms, about 200 micrograms, about 400 micrograms, about 600 micrograms and about 800 micrograms, calculated as fentanyl free base." JTX 8, col. 36, ll. 29-34.

16. Fentanyl is the active ingredient in Fentora®. D.I. 150 at 837:1-4; 998:4-16. In determining the amount of fentanyl as fentanyl free base in formulations such as Fentora® which use the salt form (fentanyl citrate), the amount must be adjusted to remove the weight of the salt (citrate). D.I. 150 at 1004:5-21. Thus, 1.57 mg of fentanyl citrate is equal to 1.0 mg (or 1000 mcg) of fentanyl calculated as fentanyl freebase. D.I. 150 at 1004:5-21; D.I. 151 at 1192:17-21.

17. Claim 1 of the '832 patent requires that the claimed tablet include "an effervescent agent comprising of food acid and a bicarbonate in an amount of about 15 to about 60 % by weight of said tablet." JTX 8, col. 36, ll. 35-37. The parties agree that an "effervescent agent" means "a compound or compounds that evolve gas by means of a reaction." D.I. 117 at 2.

18. Claim 1 of the '832 patent requires that the claimed tablet include "a pH adjusting substance comprising a carbonate in an amount of about 0.5 to about 25% by weight of said tablet, wherein said pH adjusting substance is different from the food acid and the bicarbonate in the effervescent agent." JTX 8, col. 36, ll. 38-42.

19. Claim 1 of the '832 patent requires that the claimed tablet include "a starch glycolate in an amount of about 0.25 to about 20% by weight of said tablet." JTX 8, col. 36, ll. 43-44.

20. Claim 1 of the '832 patent requires that the tablet include "mannitol in an amount of about 10 to about 80% by weight of said tablet." JTX 8, col. 36, ll. 45-46.

21. Claim 1 of the '832 patent requires that the claimed tablet be "suitable for delivery of said fentanyl across the oral mucosa of a patient by buccal administration" and that the tablet have "a dwell time that is less than about 30 minutes." JTX 8, col. 36, ll. 47-51.

22. Claim 3 of the '832 patent depends from Claims 1 and 2 and adds the limitation that the "starch glycolate is present in an amount of from about 0.5 to about 10% by weight." JTX 8, col 36, ll. 54-56.

23. Claim 4 of the '832 patent depends from Claim 1, and requires that the claimed tablet "does not include cross-linked PVP." JTX 8, col. 36, ll. 57-58. "Cross-linked PVP" or cross-linked polyvinyl pyrrolidone is also known as crospovidone. D.I. 150 at 1014:14-1015:17.

24. Claim 5 of the '832 patent depends from Claim 1, and required that the mannitol in the tablet be "spray dried mannitol." JTX 8, col. 36, ll. 59-60.

iii. <u>The Asserted Claims of the '158 Patent</u>

25. Cephalon asserted Claims 1, 15, 17, 19 and 21 of the '158 patent against Mylan.

26. Claim 1 of the '158 patent covers a "dosage form" with a particular formulation, with many of the same elements as Claim 1 of the '832 patent. Claim 1 is the only asserted independent claim of the '158 patent. JTX 6, col. 36-37.

27. Claim 1 of the '158 patent requires that the claimed dosage form include "from about 200 micrograms to about 800 micrograms of fentanyl, a salt form of fentanyl, or combination thereof, calculated as fentanyl free base." JTX 6, col. 36, ll. 36-38.

28. Claim 1 of the '158 patent requires that the claimed dosage form include "an effervescent material in an amount of about 15% to no more than about 60% by weight of the dosage form." JTX, col. 36, ll. 30-40. The parties have agreed that "an effervescent material" means "a compound or compounds that evolve gas by means of a reaction." D.I. 117 at 2. Unlike Claim 1 of the '832 patent, Claim 1 of the '158 patent does not specify the types of effervescent agents used as effervescent material.

29. Claim 1 of the '158 patent requires that the claimed dosage form include "a pH adjusting substance in an amount of about 0.5 to about 25% by weight of the dosage form, wherein said pH adjusting substance is not a component of said effervescent material." JTX 6, col. 36, ll. 41-44. The parties have a dispute, which has been fully briefed, as to the meaning of this claim element. Specifically, Mylan contends that this element of Claim 1 of the '158 patent requires that "the pH adjusting substance is not one of the components used to generate effervescence." D.I. 117 at 4. Cephalon contends that if this claim element is construed, it should be construed to mean that the "pH adjusting substance is in addition to the components of said effervescent agent." *Id*.

30. Claim 1 of the '158 patent requires that the claimed dosage form include "mannitol in an amount of between about 10 and about 80% by weight of the dosage form." JTX 6, col. 36, ll. 45-46.

31. Claim 1 of the '158 patent requires that the claimed dosage form include "a starch glycolate in an amount of about 0.25 to about 20% by weight of the dosage form." JTX 6, col. 36, ll. 47-48.

32. Claim 1 of the ‘158 patent requires that the claimed dosage form “is suitable for delivery of said fentanyl across the oral mucosa of a patient by buccal, gingival or sublingual administration.” JTX 6, col. 36, ll. 49-51.

33. Claims 15, 17, 19 and 21 of the ‘158 patent all depend from Claim 1 and add limitations specifying the amount of fentanyl, salt form of fentanyl, or combination thereof, calculated as a fentanyl free base. Specifically, claim 15 requires about 200 micrograms; Claim 17 requires about 400 micrograms; Claim 19 requires about 600 micrograms; and Claim 21 requires about 800 micrograms. JTX 6, col. 38.

B. The Prior Art and Knowledge of the Person of Ordinary Skill in the Art

i. <u>The ‘604 Patent</u>

34. The ‘604 patent issued on March 13, 2001, based on an application filed June 8, 1999. The ‘604 patent is entitled “Sublingual Buccal Effervescent.” JTX 2.

35. Because the ‘604 patent issued more than a year before the priority date for the ‘832 and ‘158 patents, there is no dispute that the ‘604 patent constitutes prior art to the ‘832 and ‘158 patents under 35 U.S.C. § 102(b).

36. Example 1 of the ‘604 patent provides as follows:

Example 1

FORMULATION	COMPONENT	QUANTITY (MG)
SHORT DISINTEGRATION TIME	Fentanyl, citrate, USP	1.57
	Lactose monohydrate	119.47
	Microcrystalline Cellulose, Silicified	119.47
	Sodium carbonate, anhydrous	46.99
	Sodium bicarbonate	105
	Citric acid, anhydrous	75
	Polyvinylphrrolidone, cross-linked	25
	Magnesium stearate	5
	Colloidal silicon dioxide	2.5
	Total tablet mass	500
LONG DISINTEGRATION TIME	Fentanyl citrate, USP	1.57
	Lactose monohydrate	270.93
	Sodium carbonate, anhydrous	40.00
	Sodium bicarbonate	105
	Citric acid, anhydrous	75
	Magnesium stearate	5
	Colloidal silicon dioxide	2.5
	Total tablet mass	500

JTX 2, col. 6, ll. 1-30.

37. Example 1 describes using 1.57 mcg of fentanyl citrate. JTX 2, col. 6, ll. 9, 21. That amount of fentanyl is the equivalent of 1000 mcg of fentanyl free base. D.I. 150 at 1004:5-21; D.I. 151 at 1192:17-21.

38. The '604 patent describes and claims using a "pharmaceutically effective amount" of an oral medicament in the effervescent formulations. JTX 2, col. 7, ll. 14-23. The person of ordinary skill in the art would have understood that a "pharmaceutically effective amount" of fentanyl included dosages within the claimed ranges. D.I. 150 at 1005:13-1006:7. At the time of the alleged invention, fentanyl for delivery through the oral mucosa was already commercially available in the Actiq® product at a range of dosages from 200 to 1600 mcg. D.I. 150 at 1022:21-1023:16; D.I. 148 at 331:3-16.

39. To the extent that the person of ordinary skill in the art was not aware of the specific amounts of fentanyl that were pharmaceutically effective, such person would have found that information readily in the literature based on the commercially available dosages of fentanyl in clinical use. D.I. 150 at 1022:21-1023:4.

40. The person of skill in the art would have been motivated by the '604 patent's teaching to use a pharmaceutically effective amount of fentanyl to look to other art to establish the specific dosages that constitute pharmaceutically effective amounts of fentanyl. D.I. 150 at 1023:21-1024:4.

41. Example 1 of the '604 patent describes tablets containing fentanyl as the active ingredient, along with sodium carbonate, sodium bicarbonate and citric acid. JTX 2, col. 6, ll. 1-20. The formulation described in Example 1 of the '604 patent includes both effervescent materials and a pH adjusting substance to raise the pH. D.I. 150 at 1006:20-1007:9; 1011:7-13.

42. The '604 patent describes, in Example 1 and elsewhere in the specification, an effervescent agent comprising a food acid and a bicarbonate. JTX 2, col. 6, ll. 1-20; col. 2, ll. 53-61. Specifically, Example 1 of the '604 patent contains citric acid and sodium bicarbonates. *Id*. at col. 6, ll. 1-20. Citric acid is a food acid and sodium bicarbonate is (of course) a bicarbonate. D.I. 150 at 1007:7-9.

43. The citric acid and sodium bicarbonate used in Example 1 of the '604 patent constitute 36 percent of the weight of the tablet, which is within the range of about 15 to about 60 percent. JTX 2, col. 6, ll. 1-2.

44. The '604 patent describes in Example 1 a tablet that contains between 9 and 10 percent sodium carbonate. JTX 2, col. 6, ll. 13-14. That sodium carbonate contains excess carbonate that would act to adjust the pH, and is neither the food acid nor the bicarbonate. D.I. 150 at 1011:7-13.

45. The '604 patent states that "[n]on-limiting examples of suitable fillers include: **mannitol**, dextrose, lactose, sucrose, and calcium carbonate." JTX 2, col. 5, ll.29-32 (emphasis added).

46. The effervescent tablets described in Example 1 of the '604 patent contain lactose monohydrate as a filler. JTX 2, col. 6, ll. 1-20. Lactose was an inexpensive filler commonly used in pharmaceutical formulations at the time of the alleged invention. D.I. 150 at 1031:16-1032:3; DTX 720 at 276 ("Lactose is widely used as a filler or diluent in tablets, capsules. . . .").

47. Example 2 of the'604 patent describes a buccal formulation using a different active ingredient than Example 1, and using mannitol as the filler. JTX 2, col.6, l. 33 - col. 7 l. 10. Example 2 of the '604 patent describes a tablet formulation where mannitol is used in an amount of 11.67 percent of the tablet weight. JTX 2, col 6, ll.59; D.I. 151 at 1076:10-14.

48. The '604 patent describes the suitability of a number of non-effervescent disintegration agents expressly as follows:

> Non-limiting examples of non-effervescent disintegration agents include: microcrystalline cellulose, croscarmelose sodium, crospovidone, starches, corn starch, **potato starch and modified starches thereof**, sweeteners, clays such as bentonite, alginates, gums such as agar, gar, locust bean, karaya, pecitin and tragacanth."

JTX 2, col. 4, ll. 41-51 (emphasis added).

49. There is no dispute that sodium starch glycolate is a modified potato starch. D.I. 151 at 1196:18-22; 1079:8-9; 1098:24-1099-7. Sodium starch glycolate is the only modified potato starch that is used as a disintegrant in pharmaceutical products. D.I. 150 at 1013:13-22; D.I. 151 at 1077:21-25.

50. The '604 patent further specifies that non-effervescent disintegrant agents "may comprise up to about 20 weight percent and preferably between about 2 and about 10% of the total weight of the composition." *Id*. at col. 4, ll. 49-51.

51. Example 1 of the '604 patent includes in its "short disintegration time" formulation the disintegrant known as crospovidone (referred to in the example as "polyvinylphrrolidone [sic], cross-linked"). JTX 2, col. 6, ll. 16-17; D.I. 151 at 1215:8-12.

Crospovidone is considered by formulators to be a member of the separate class of disintegrants that formulators consider superdisintegrants. D.I. 151 at 1215:8-12; D.I. 150 at 1015:6-11.

52. The person of ordinary skill in the art understood at the time of the alleged invention that crospovidone was a superdisintegrant. D.I. 150 at 1015:6-11; D.I. 150 at 940:3-5; D.I. 148 at 329:7-10; D.I. 151 at 1215:13-16. The person of ordinary skill in the art also would have understood that there were three (or at most four) superdisintegrants used in pharmaceutical formulations: crospovidone, sodium starch glycolate, and croscarmelose sodium. D.I. 150 at 1015:6-11; D.I. 151 at 1215:13-22. (Dr. Illum suggesting that there might be a fourth).

53. The '604 patent, in the examples and elsewhere in the specification, describes a tablet suitable for delivering fentanyl across the oral mucosa by buccal administration. JTX 2, col. 6, l. 53 (describing buccal formulation in example); col. 5, lines 49-54 (describing dosage form being administered by placement "adjacent to a cheek (for buccal administration)").

54. The '604 patent, in Example 1 and elsewhere in the specification, describes tablets that have a dwell time that is less than about 30 minutes. D.I. 150 at 1021:7-24; PTX 317 at 7; PTX 456 at 6. It is undisputed that Cephalon's testing showed that the formulation described in Example 1 of the '604 patent had a dwell time that is less than about 30 minutes. *Id*.; DTX PTX 317 at 7; PTX 456 at 6.

ii. <u>The Knowledge of Persons of Ordinary Skill in the Art Relating to Pharmaceutically Effective Dosages of Fentanyl.</u>

55. Each of the elements of the asserted claims that Cephalon contends is not disclosed by the '604 patent was readily known to the person of ordinary skill in the art at the time of the alleged invention of the '832 and '158 patents.

56. The Actiq® product was commercially available at the time of the alleged invention. D.I. 151 at 1217:9-15. Like the Fentora® product, Actiq® delivers fentanyl through

the oral mucosa to treat breakthrough cancer pain. D.I. 147 at 100:18-21 (Actiq® indicated for treatment of breakthrough cancer pain); D.I. 151 at 1217:9-18; DTX 586 at 1. The Actiq® package insert describes fentanyl dosages ranging from 200 mcg to 1600 mcg, measured as the free base. PTX 472 at 7-8; DTX 586 at 1; D.I. 151 at 1204:6-9; D.I. 147 at 100:22-101:9. The starting dose for patients using Actiq® is 200 mcg of fentanyl. D.I. 147 at 100:22-101:9.

57. A person of ordinary skill in the art would have been familiar with the Actiq® product. D.I. 151 at 1204:4-9; D.I. 148 at 295:19-25.

58. Each of the specific dosages claimed in claims 15, 17, 19 and 21 of the '158 patent was also a dosage that a skilled person in the art would have understood at the time was an available Actiq® dosage. D.I. 150 at 1022:23-1023:16; DTX 472 at 7-8; DTX 586 at 1.

59. Cephalon's witnesses did not dispute that the claimed dosages of Actiq® were known by the person of ordinary skill in the art to be pharmaceutically effective dosages of fentanyl. D.I. 151 at 1217:19-23. Indeed, Dr. Moe testified that a starting point for figuring out what doses to use for delivery of a therapeutically effective amount of fentanyl was the Actiq® doses that were already commercially available. D.I. 148 at 330:22-331:7.

60. The person of ordinary skill in the art would have been motivated to look at the Actiq® product (and its package insert) based on the express teaching of the '604 patent that the effervescent formulations described therein should contain "a pharmaceutically effective amount" of the medicament being used. JTX 2, col. 7, ll. 15-23; D.I. 150 at 1023:21-1024:4.

iii. <u>The Prior Art and Knowledge of the Person of Ordinary Skill in the Art Relating to Mannitol.</u>

61. The '604 patent's disclosure of mannitol as a suitable filler would have motivated the person of ordinary skill in the art to consult pharmaceutical references for information concerning the properties and utility of mannitol. D.I. 150 at 1033:4-13 (explaining that the '604

patent "clearly allows use of mannitol" and the information in the prior art would indicate that it would be the correct choice).

62. The person of ordinary skill in the art would have had readily available information concerning the characteristics of mannitol from references such as the Handbook of Pharmaceutical Excipients. DTX 722; D.I. 150 at 1033:4-13. The Handbook of Pharmaceutical Excipients contained a monograph providing detailed information about the characteristics of mannitol and its use as a filler in pharmaceutical products. DTX 722; D.I. 150 at 1031:3-7.

63. The person of ordinary skill in the art would have known that mannitol was commonly used as a filler in chewable tablets and other pharmaceutical formulations that are designed to be retained in the mouth rather than swallowed. *See* D.I. 148 at 321:9-18; D.I. 150 at 1016:20-1017:1 DTX 722 at 324 (describing common use of mannitol in chewable tablets). Dr. Moe confirmed that at the time of his alleged invention mannitol was a fairly common ingredient in chewable tablets. D.I. 148 at 321:9-18. Mannitol has the desirable feature of feeling cool in the month as it dissolves, which makes it particularly useful for tablets that are intended to dissolve in the mouth. D.I. 148 at 321:9-18; D.I. 150 at 1016:20-1017:1.

64. It was known that lactose, the filler used in the earlier CIMA formulation, was subject to the Maillard reaction, a reaction that causes browning. D.I. 148 at 320:7-15; D.I. 150 at 1032:7-23; D.I. 150 at 1031:14-1033-3. It was known that mannitol is not subject to the Maillard reaction. D.I. 148 at 320:19-21; DTX 722 at 5; DTX 722 at 326 ("Mannitol does not undergo Maillard reactions").

65. Cephalon's expert, Dr. Lisbeth Illum conceded that nothing in the '604 patent teaches away from using mannitol as a filler in a fentanyl formulation. D.I. 151 at 1212:6-12.

66. The Handbook of Pharmaceutical Excipients provided additional information concerning the properties of mannitol that would have further supported its choice as a filler in the formulations described in the '604 patent. In particular, the Handbook describes the fact that mannitol does not participate in the Maillard reaction. DTX 722 at 327; D.I. 150 at 1033:4-13. The person of ordinary skill in the art would have understood that the Maillard reaction could cause stability issues in various formulations depending on the chemical makeup of the active ingredient and other components of the formulation. D.I. 150 at 1032:7-1033:3.

67. The Handbook of Pharmaceutical Excipients also provides the person of ordinary skill in the art information concerning the properties of lactose as a filler. DTX 720. The Handbook indicates that lactose is subject to the Maillard reaction. DTX 720 at 283.

68. It is undisputed that the claimed range of mannitol is a typical range for the amount of mannitol in a tablet. D.I. 148 at 344:3-11; D.I. 151 at 1210:4-7.

69. There would not have been anything unusual about choosing to use mannitol and sodium starch glycolate together in a formulation. D.I. 150 at 1033:14-18. Both of these excipients were widely used in tablet formulations at the time of the alleged inventions. *See* DTX 723 at 501 (sodium starch glycolate widely used as disintegrant in tablet formulations); DTX 722 at 324 (mannitol widely used in tablet formulations).

iv. <u>The Prior Art and Knowledge of Person of Ordinary Skill in the Art Relating to Starch Glycolate.</u>

70. The person of ordinary skill in the art would have been motivated to look to the Handbook of Pharmaceutical Excipients based on the '604 patent's disclosure of suitable non-effervescent disintegrants for use in the formulations described therein. D.I. 150 at 1027:1-19.

71. The Handbook of Pharmaceutical Excipients describes all of the disintegrants approved for use in pharmaceutical products. D.I. 150 at 997:7-17.

72. The Handbook of Pharmaceutical Excipients also provides a description of the properties of the various disintegrants. *See, e.g.*, DTX 723. There is no dispute that the Handbook of Pharmaceutical Excipients identified at the relevant time only three superdisintegrants: crospovidone, croscarmelose sodium, and sodium starch glycolate. D.I. 151 at 1215:13-16; DTX 737 at 651.

73. The Handbook of Pharmaceutical Excipients' entry for sodium starch glycolate confirms that sodium starch glycolate is a modified potato starch. DTX 723 at 503.

74. It was known that crospovidone, the superdisintegrant used in the original CIMA formulation, contains peroxides. D.I. 148 at 325:8-18; D.I. 151 at 1213:15-1215:1 (formulators and the person of ordinary skill in the art knew prior to the work on the Moe patents that crospovidone contained peroxides). It was also known that peroxides could contribute to degradation problems. D.I. 151 at 1213:8-14; 1029:4-20.

75. Sodium starch glycolate was commercially available as a superdisintegrant at the time of the alleged invention. D.I. 148 at 325:19-326:14. It was known at the time of the alleged invention that sodium starch glycolate did not contain peroxides. D.I. 148 at 329:4-6. Thus, the person of ordinary skill in the art also would have understood that sodium starch glycolate, in contrast to crospovidone, did not contain peroxides. D.I. 150 at 1027:13-16.

76. It is undisputed that the claimed ranges for amounts of sodium starch glycolate are typical for a disintegrant in a tablet. D.I. 148 at 343:28-344:2 (inventor Moe testifying that the claimed range is typical range for disintegrant in a tablet). D.I. 151 at 1210:8-10.

77. The claimed ranges are broader in scope than the typical amount of sodium starch glycolate. *See* DTX 723 at 501 (usual concentration is 2-8%); D.I. 151 at 1235:19-1236:13.

C. The Development of the Mannitol/Sodium Starch Glycolate Formulation at Cephalon (CIMA)

78. Prior to Dr. Moe's involvement, the dosages of fentanyl being used in the earlier lactose/crospovidone formulation were in the same range as that claimed in the '832 and '158 patents. *See* DTX 199 at 28-29; D.I. 148 at 291:13-292:16. Those dosages included dosages below 880 mcg. D.I. 148 at 292:3-16.

79. The dosages used in the development of the formulation that became Fentora® were based on the dosages used in the Actiq® product that was already commercially available and well known to persons skilled in the art. D.I. 148 at 331:3-7; D.I. 151 at 1217:19-23; D.I. 150 at 1022:23-1023:16.

80. The testing that had been done on the lactose/crospovidone formulation, before the alleged inventions of the '832 and '158 patent, showed that it would have increased bioavailability over Actiq®. D.I. 148 at 291:18-22.

81. Stability testing is a routine part of drug development and is required by the FDA. D.I. 151 at 1212:23-1213:7.

82. During routine stability testing, the formulation developed by CIMA was found to have mottling (*i.e.*, the tablets developed brown spots over time). D.I. 148 at 319:19-320:6; DTX 199 at 30.

83. Cephalon informed the FDA that the formulation change from lactose to mannitol was necessary to address the browning of the tablets. DTX 199 at 30; D.I. 148 at 323:23-324:10. Dr. Moe agreed that the result of changing the filler from lactose to mannitol was the elimination of the browning problem. D.I. 148 at 324:16-325:1. Dr. Illum also recognized that CIMA concluded that the switch to mannitol solved the tablet browning problem. D.I. 151 at 1212:13-66.

84. Dr. Moe had worked with mannitol as a filler for other projects prior to his work on fentanyl tablets. D.I. 148 at 320:25-321:8.

85. During the development of the claimed formulation, CIMA did not test any formulation with fillers other than lactose and mannitol. D.I. 148 at 321:19-322:14. As CIMA informed the FDA, the switch of fillers from lactose to mannitol fixed the mottling problem with the tablets. DTX 199 at 30; D.I. 148 at 323:24-325:1.

86. During routine FDA-mandated stability testing, the formulation developed by CIMA was found to have increasing related substances (*i.e.*, the fentanyl was degrading). DTX 199; D.I. 148 at 325:2-7; D.I. 151 at 1212:23-1213:2.

87. At the time, persons of ordinary skill knew that crospovidone contained peroxides that could cause degradation of pharmaceutical compounds. D.I. 148 at 325:8-18; D.I. 151 at 1213:15-1215:1. Sodium glycolate was known not to contain peroxides. D.I. 150 at 1027:13-16.

88. Dr. Moe had worked with sodium starch glycolate as a disintegrant prior to the alleged invention. D.I. 148 at 326:8-14.

89. Sodium starch glycolate and crospovidone were the only super disintegrants that were in CIMA's GMP (good manufacturing practices) system. D.I. 148 at 326:15-22.

90. CIMA did not test any formulation with non-effervescent disintegrants other than crospovidone and sodium starch glycolate. D.I. 148 at 329:7-14.

91. As CIMA informed the FDA, the switch from crospovidone to sodium starch glycolate solved the degradation problem. DTX 199 at 30; D.I. 148 at 327:21-328:19.

D. Cephalon's Evidence of Unexpected Benefits Is Not Commensurate with the Scope of the Claims

92. The asserted claims of the '832 patent cover a range of fentanyl dosages from about 100 to about 800 mcg. JTX 8, col. 36. The asserted claims of the '158 patent cover a

range of fentanyl dosages from about 200 to about 800 mcg. JTX 6, col. 36. Dependent claims 15, 17, 19 and 21 cover specific dosages of about 200 mcg, about 400 mcg, about 600 mcg and about 800 mcg. JTX 6, col. 36.

93. Dr. Jerling's assertion that there are unexpected benefits is based solely on testing of the 810 mcg dose. D.I. 151 at 1158:12-21. Even if Cephalon's arguments for unexpected benefits of higher blood levels were correct, those alleged benefits were not seen at either lower dosages (the 270 mcg dose) or higher dosages (the 1080 mcg dose and the 1300 mcg dose). D.I. 150 at 1042:23-1043:9; D.I. 151 at 1172:15-19.

94. The asserted independent claims of the '832 and '158 patent both cover a range of mannitol in the formulation from about 10 to 80% of the weight of the tablet. JTX 6, col. 36, ll. 45-46; JTX 8, col. 36, ll. 46-47.

95. The only data on which Cephalon relies to show alleged unexpected benefits relates to testing on formulations with approximately 47-49% mannitol. D.I. 148 at 338:16-339:25; D.I. 151 at 1236:22-24. No pharmacokinetic testing has been done and Cephalon has no data concerning the pharmacokinetic results for any formulations containing mannitol at any point in the claimed range above or below the 47-49% range. D.I. 148 at 338:16-39:25.

96. Cephalon has pointed to no evidence that the results seen with a formulation containing 47-49% mannitol would be the same for a formulation with less or more mannitol within the claimed ranges, and there is none in the record. The fact that those claimed ranges include amounts of mannitol that are typically used in pharmaceutical formulations do not provide any evidence as to whether the alleged unexpected benefits would occur at other amounts of mannitol. Cephalon argues that the alleged results that they claim to see—enhanced drug delivery at a single dosage—are surprising, *i.e.*, not typical. *See* D.I. 151 at 1126:9-17;

1209:9-15. There is no evidence that this surprising, non-typical result, if it exists, would occur over a wide range of concentrations that are "typical" for mannitol when used for its typical function as a filler. *See* D.I. 151 at 1171:23-1172:4; 1236:17-1237:7.

97. Claim 1 of the '832 and '158 patents both cover mannitol without regard to whether or not it is spray dried mannitol. JTX 6, col. 36, ll. 45-46; JTX 8, col. 36, ll. 46-47. All of the formulations on which Cephalon bases its unexpected benefits included spray dried mannitol. D.I. 148 at 339:5-8. Spray dried mannitol was the form most commonly used in the formulation of compressed tablets. D.I. 150 at 1018:14-22. No testing has been done as to the pharmacokinetics of any form of mannitol other than spray dried mannitol. D.I. 148 at 339:5-8.

98. The asserted independent claims of the '832 and '158 patents cover a range of the amount of a starch glycolate from 0.25% to 25%. JTX 6, col. 36, ll. 47-48; JTX 8, col. 36, ll. 43-44. Dependent Claim 3 of the '832 patent covers a range of the amount of a starch glycolate from 0.5 to 10%. JTX 8, col. 36, ll. 54-56.

99. The only data on which Cephalon relies to show the alleged unexpected benefits is from a formulation containing 3% sodium starch glycolate. D.I. 148 at 337:11-23.

100. There have been no pharmacokinetic studies done on any formulations with less or more than 3% sodium starch glycolate. D.I. 148 at 337:11-338:15; D.I. 151 at 1171:6-16 (all formulations studied had same amounts of components).

101. There is no evidence concerning whether the results seen for 3% sodium starch glycolate would be the same for a formulation with less or more starch glycolate within the claimed ranges. *See* D.I. 151 at 1171:23-1172:4. The fact that those claimed ranges include amounts of starch glycolate that are typically used in pharmaceutical formulations do not provide any evidence as to whether the unexpected benefits that Cephalon claims would occur at other

amounts of starch glycolate across the claimed range. *See* D.I. 151 at 1235:1-1236:13. There is no evidence that the alleged surprising results -- enhanced fentanyl delivery would occur over the broad range of concentration of starch glycolate claimed. *See* D.I. 151 at 1235:1-1236:13.

102. There is no evidence of whether mannitol, starch glycolate, or a specific combination in ratios used is responsible for the alleged benefits. D.I. 148 at 336:17-337:3; D.I. 151 at 1171:17-22.

E. The Evidence Does Not Show Any Unexpected Benefits of the Invention of the '832 And '158 Patents

103. The only evidence in the record concerning unexpected benefits of the invention of the '832 and '158 patents relates to the measurement of the blood plasma concentrations associated with the mannitol/sodium starch glycolate formulation as opposed to the lactose/crospovidone formulation. *See, e.g.*, D.I. 151 at 1126:12-17.

104. The unexpected benefit claimed by Cephalon is a higher maximum plasma concentration, referred to as Cmax, and a higher area under the curve for the first hour after administration. D.I. 151 at 1126:12-17. Cephalon asserts that the formulation using mannitol and sodium starch glycolate instead of lactose and crospovidone reaches higher levels of fentanyl in the blood at the same dosage of fentanyl. *Id*.

105. There are no head-to-head studies comparing the blood plasma fentanyl levels associated with the lactose/crospovidone formulation to those associated with the mannitol/sodium starch glycolate formulation. D.I. 148 at 299:14-19; D.I. 151 at 1159:6-91; D.I. 151 at 1164:12-15. Two of the three comparisons made by inventor Moe in his declaration to the Patent Office show no statistically significant difference between the two formulations even at the less stringent 0.05 confidence level. D.I. 150 at 1043:10-18.

106. With respect to the 1300 mcg dosages, the lactose/crospovidone formulation showed a higher Cmax than the mannitol/sodium starch glycolate formulation—the opposite of the effect argued by Cephalon. D.I. 148 at 301:24-302:3.

107. Cephalon's assertion of unexpected benefits is based only on the results for a single dosage, 810 mcg, in one study (the 99-11 study), conveniently ignoring all other results. D.I. 151 at 1168:15-1170:18. In that study, the 810 mcg formulation was administered to a total of only **13** subjects. D.I. 151 at 1163:11-19. The 99-11 study was not designed to compare the pharmacokinetics for the mannitol/starch glycolate formulation to the lactose/crospovidone formulation. *See* D.I. 151 at 1225:12-20 (studies were designed to get the answer to a different question and are "being twisted to get an answer for a question they didn't ask").

108. It is not appropriate to compare pharmacokinetic data from separate studies and conclude from that comparison that one formulation is better than another. D.I. 150 at 1037:21-1038:19; 1045:9-1046:16. There is tremendous variability between individuals with respect to the plasma levels achieved for these formulations. *See, e.g.*, PTX 261 at 51 (showing maximum and minimum plasma levels); D.I. 151 at 1130:18-25; 1163:6-10 (fentanyl displayed moderate pharmacokinetic variability); D.I. 150 at 1037:21-1038:19. Using data from two different studies in different subjects means that the differences in the plasma levels may be due to differences in the individual subjects rather than any real difference in the formulation. D.I. 150 at 1038:9-15.

109. The pitfalls of plucking data from two different studies and then looking for significant differences between the results is illustrated by the results for the 810 mcg dosage in two of the Cephalon studies. As Dr. Kibbe explained, when one compares the results of two

Cephalon studies of the very same tablets, *i.e.*, tablets with the same formulation from the same lot of tablets, one finds a statistically significant difference. D.I. 151 at 1227:9-1228:15.

F. Objective Indicia of Non-Obviousness Have Not Been Established and Cannot Overcome the Showing of Obviousness

110. In addition to the evidence of unexpected results discussed *supra*, Cephalon has also come forward with evidence purporting to show the objective indicia of copying and commercial success.

111. With respect to copying, Cephalon relies solely on the evidence concerning the similarity of the Mylan formulation and the brand name formulation. *See, e.g.*, D.I. 151 at 1208:16-1209:8. There was no evidence in the record at trial that the allegedly novel aspects of the inventions of the '832 and '158 patents over the prior art was what led Mylan to its formulation. Indeed, to the extent there was any evidence presented relating to the issue of copying, it related to the adoption of effervescence by Mylan. *See, e.g.*, D.I. 151 at 1208:9-19. There is no dispute that the '604 patent taught the use of effervescent formulations for the delivery of fentanyl. D.I. 149 at 546:18-25; 547:18-20; 550:16-20. Cephalon cannot use the alleged failure of Mylan to develop a non-effervescent formulation (which is the evidence on which Dr. Illum relies, *see* D.I. 151 at 1208:9-19) as evidence to support its copying argument when it is undisputed that the use of an effervescent formulation was in the prior art for the alleged inventions of the '832 and '158 patents.

112. With respect to commercial success, Cephalon relies on evidence concerning the sales of the Fentora® commercial product. Fentora® competes in the transmucosal immediate release fentanyl (or "TIRF") market. D.I. 151 at 1105:6-15.

113. Before 2006, Actiq® was the only product in the TIRF market. D.I. 151 at 1106:12-17. The Actiq® product and its generics hold more than twice the total prescription market share than Fentora® in that market. D.I. 151 at 1116:15-18.

114. There is no evidence tying the asserted commercial success of the Fentora® product to any of the features of the invention of the '832 and '158 patents. *See* D.I. 151 at 1112:2-1113:14. None of Cephalon's experts made any effort to attribute the commercial success of the Fentora product to the alleged inventions of the '832 and '158 patents versus the prior art '604 and '590 patents. *See, e.g.*, D.I. 151 at 1211:16-18 (Dr. Illum relies on Dr. Snell); D.I. 151 at 1116:19-1117:11 (Dr. Snell has not attributed commercial success specifically to '832 and '158 patents). Indeed, Cephalon's experts agreed that it was the inventions of the '604 and '590 patents that enabled the Fentora® product to become commercially available. D.I. 147 at 113:5-16; D.I. 147 at 133:14-134:13; D.I. 151 at 1117:9-20.

115. Dr. Snell, Cephalon's expert on commercial success, testified only in general terms that it was the "formulation and method of administration" of Fentora® that is covered by the patents-in-suit. D.I. 151 at 1112:10-1113:5. Indeed, he specifically referred to the four patents in suit (the '832 and '158 patent and the '590 and '604 patents) and then testified broadly that there is a nexus "between Fentora's commercial success and the patents-in-suit." D.I. 151 at 1113:6-7. He did not even attempt to explain to what extent, if any, the alleged commercial success is attributable to the '832 and '158 patents as opposed to the prior art '604 and '590 patents. D.I. 151 at 1116:19-1117:11.

116. The '604 patent was listed in the Orange Book as a patent covering the Fentora® commercial product at the time of the alleged inventions of the '832 and '158 patents. D.I. 147 at 113:5-11.

MYLAN'S PROPOSED CONCLUSIONS OF LAW

I. THE ASSERTED CLAIMS OF THE '832 AND '158 PATENTS ARE ANTICIPATED BY THE '604 PATENT

A. Governing Law of Anticipation

1. To anticipate a patent claim under 35 U.S.C. § 102, a prior art reference "must describe . . . each and every claim limitation" of the claimed invention. *Clearvalue, Inc. v. Pearl River Polymers, Inc.*, 668 F.3d 1340, 1344 (Fed. Cir. 2012); *see also In re Schreiber*, 128 F.3d 1473, 1477 (Fed. Cir. 1997). Moreover, for a prior art reference to anticipate a claim it must disclose all of the claim limitations "arranged or combined in the same way as in the claim." *Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1361 (Fed. Cir. 2012).

2. The party challenging the validity of a patent bears the burden of establishing invalidity by clear and convincing evidence. *Microsoft Corp. v. i4i Ltd. P'ship*, 131 S. Ct. 2238, 2242 (2011).

3. In analyzing whether a reference is anticipatory, the reference must be viewed as it would have been understood by a person of ordinary skill in the field of the invention. *See Retractable Technologies, Inc. v. Becton, Dickinson and Company*, 653 F.3d 1296, 1309 (Fed. Cir. 2011) ("For a prior art reference to anticipate a patent claim, the reference, as read by one of ordinary skill in the art, must disclose each claim limitation"); *AT&T Corp. v. Excel Comm'n, Inc.*, No. 96-434-SLR, 1999 WL 1050064 at *18 (D. Del. Oct. 25, 1999). To discern how the person of ordinary skill in the art would have understood the disclosures of a reference, extrinsic evidence may be considered "when it is used to explain, but not expand, the meaning of a reference." *In re Baxter Travenol Labs.*, 952 F.2d 388, 390 (Fed. Cir. 1991) (holding that it was appropriate to look to extrinsic evidence to determine the chemical properties of a disclosed

commercial brand bag for purposes of an anticipation inquiry); *AT&T Corp.*, 1999 WL 1050064 at *18 (“Extrinsic evidence may be appropriate ‘to explain the disclosure of a reference.’”).

4. When a patent claims a range of elements, any single prior art reference that falls within the range anticipates the claim. *See Titanium Metals Corp. v. Banner*, 778 F.2d 775, 780-82, 227 U.S.P.Q. (BNA) 773, 778 (Fed. Cir. 1985) ("It is also an elementary principle of patent law that when, as by a recitation of ranges or otherwise, a claim covers several compositions, the claim is ‘anticipated’ if one of them is in the prior art.").

5. When a claim is limited to a combination of components, each of which is disclosed in lists in a prior art reference, the question for anticipation is “whether the number of categories and components” is so large that the claimed combination “would not be immediately apparent to one of ordinary skill in the art.” *Wm. Wrigley Jr. Co.*, 686 F.3d at 1361; s*ee also Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1377 (Fed. Cir. 2005) (distinguishing cases where prior art discloses a genus from those in which it discloses a number of species as part of a list). In addressing this question, the Court may look at evidence that would direct the skilled person to selection of the claimed component. *Id.* (Shahidi reference clearly identifies the combination of WS-23, which Shahidi identifies as one of three preferred cooling agents, and menthol, which Shahidi identifies as being among the “most suitable” flavoring ingredients.)

6. Allegations of unexpected results are irrelevant to anticipation. *See In re Wiggins*, 488 F.2d 538, 543 (C.C.P.A. 1973). “No matter how striking,” evidence of secondary considerations cannot overcome a finding of anticipation. *Id.; see also Cohesive Techs., Inc.*, 543 F.3d 1351, 1364 (Fed. Cir. 2008) (secondary considerations not element of anticipation).

7. In determining the skill level of the person of ordinary skill in the art, “the court may consider various factors including ‘type of problems encountered in the art; prior art

solutions to those problems; rapidity with which innovations are made; sophistication of the technology; and educational level of active workers in the field.'" *In re GPAC Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995) (internal citations omitted).

8. The person of ordinary skill in the art to whom the '832 and '158 patents are directed is someone with a Ph.D. in pharmaceutics or a similar discipline, and a few years of experience, especially with oral solid dosage forms or solid dosage forms for buccal administration. D.I. 150 at 998:20-999:25.

9. Even under the definition of the person of ordinary skill advanced by Cephalon, that person would have years of experiences in developing transmucosal drug delivery systems and, therefore, have the same knowledge concerning the development of such systems as the person of ordinary skill under Mylan's proposed definition. D.I. 148 at 534:6-19 (definition of person of ordinary skill in the art includes three or more years of experience in developing transmucosal drug delivery systems). Therefore, the invalidity analysis would be essentially the same for the person of ordinary skill in the art under either of the proffered definitions.

B. Mylan Has Shown By Clear and Convincing Evidence That Claim 1 of the '832 Patent Is Anticipated By the '604 Patent

i. <u>The claim limitations that are not in dispute</u>

10. As Mylan's expert Dr. Kibbe explained in detail, each of the elements of claim 1 of the '832 patent is disclosed by the '604 patent. *See* D.I. 150 at 1002:1-1022:4. Although many of these disclosures are not in dispute, Mylan addresses each element herein, before turning to those elements of Claim 1 that Cephalon's expert witness, Dr. Illum, asserts are not disclosed by the '604 patent.

11. Claim 1 of the ‘832 patent requires that the tablet containing an effervescent agent, which includes a food acid and a bicarbonate, in an amount from about 15-60% of the weight of the tablet. JTX 8, col. 36, ll. 36-38.

12. The ‘604 patent describes, in Example 1 and elsewhere in the specification, a tablet with an effervescent agent comprising a food acid and a bicarbonate. Specifically, Example 1 of the ‘604 patent contains citric acid and sodium bicarbonates. JTX 2, col. 6, ll.14-15. The specification of the ‘604 patent specifically describes the use of food acids and preferably sodium bicarbonate as the effervescent agent. *Id*. at col. 2, ll. 41-61. Citric acid is a food acid and sodium bicarbonate is (of course) a bicarbonate. D.I. 150 at 1007:8-9.

13. The citric acid and sodium bicarbonate used in Example 1 of the ‘604 patent constitute 36 percent of the weight of the tablet, which is within the range of about 15 to about 60 percent. JTX 2, col. 6, ll. 1-2, 14-15; D.I. 150 at 1006:12-1007:6.

14. Claim 1 of the ‘832 patent requires a carbonate pH adjusting substance that is (1) between about 0.5 to about 25% of the weight of the tablet and (2) that the carbonate is different than the food acid and bicarbonate in the formulation. JTX 8, col. 36, ll. 38-42.

15. The ‘604 patent describes in Example 1, a tablet that contains between 9 and 10 percent sodium carbonate. JTX 2, col. 6, ll. 12-13; D.I. 150 at 1010:7-1011:13. That sodium carbonate is not either the food acid or the bicarbonate. D.I. 150 at 1011:7-13.

16. Claim 1 of the ‘832 patent requires that the tablet be suitable for delivery of fentanyl through the oral mucosa by buccal administration. JTX 8, col. 36, ll. 47-51.

17. The ‘604 patent, in Example 1 and elsewhere in the specification, describes a tablet suitable for delivering fentanyl across the oral mucosa by buccal administration. The ‘604 patent specifically describes buccal formulations. *See, e.g.*, JTX 2, col. 5, ll. 49-54 (describing

placing the dosage form in the mouth and holding it adjacent to the cheek for buccal administration). The person of ordinary skill in the art would understand the '604 patent to be describing buccal administration. D.I. 150 at 1019:4-16.

18. Claim 1 of the '832 patent requires that the tablet have a dwell time of less than about 30 minutes. JTX 8, col. 36, ll. 47-51.

19. The '604 patent, in Example 1 and elsewhere in the specification, describes tablets that have a dwell time that is less than about 30 minutes. Dwell time is the amount of time the tablet stays in residence in the site of administration. D.I. 150 at 1019:21-23. It was undisputed that the formulation described in Example 1 of the '604 patent has a dwell time of less than about 30 minutes. D.I. 150 at 1021:7-24; PTX 317 at 7; PTX at 456 at 6. Moreover, the '604 patent incorporates by reference with respect to the tablets U.S. Patent No. 5,223,264, which teaches the use of short dwell times of less than 30 minutes. D.I. 150 at 1020:17-1021:6; DTX 413 at col. 6, ll. 5-12.

ii. Fentanyl amounts

20. Claim 1 of the '832 patent requires that the tablet contain an amount of fentanyl between 100 and 800 mcg, measured as the fentanyl free base. JTX 8, col. 36, ll. 29-34. Although the '604 patent teaches the use of a "pharmaceutically effective amount" of fentanyl, Cephalon's expert, Dr. Illum, nevertheless asserts that the '604 patent does not disclose this limitation to the person of ordinary skill in the art. D.I. 151 at 1187:2-7.

21. The '604 patent discloses to the person of ordinary skill in the art buccal dosage forms and tablets comprising fentanyl within the range claimed in the '832 patent. D.I. 150 at 1005:15-1006:7. The '604 patent teaches using "a pharmaceutically effective amount of an orally administered medicament." *See* JTX 2, claim 1; D.I. 150 at 1003:11-16.

22. Example 1 of the '604 patent provides for two fentanyl formulations. *See* JTX 2, col. 6, ll. 1-3; D.I. 150 at 1003:5-10. The amount of fentanyl in Example 1 of the '604 patent is 1,570 mcg of fentanyl citrate or approximately 1,000 mcg of fentanyl free base. D.I. 150 at 1004:16-21; D.I. 151 at 1192:15-21.

23. There is no dispute that amounts of fentanyl ranging from 100 to 800 mcg are, in fact, pharmaceutically effective. *See, e.g.,* D.I. 148 at 295:19-25 (doses from 100 to 800 mcg fentanyl showed clinical efficacy).

24. Dr. Kibbe, an expert in the field of pharmaceutics including drug formulation, testified that a person of ordinary skill in the art would have understood the '604 patent's disclosure of a pharmaceutically effective amount of fentanyl to include the claimed amounts of fentanyl ranging from 100 to 800 mcg. D.I. 150 at 1005:21-24.

25. The '604 patent's explicit disclosure of fentanyl coupled with its disclosure of a "pharmaceutically effective amount of an orally administered medicament" would, when viewed from the perspective of a person of ordinary skill at the time, have anticipated the amounts and ranges of fentanyl claimed in Claim 1 of the '832 patent. The Federal Circuit has specifically instructed that in regard to interpreting the term "pharmaceutically effective amount," one may look at what the person of ordinary skill in the art would have understood such amounts to be. *See Key Pharms. v. Hercon Labs. Corp.*, 161 F.3d 709, 717 (Fed. Cir. 1998) ("[I]t is quite sensible to look to the FDA to determine what amounts are considered pharmaceutically effective.") As Cephalon's witnesses must concede, a person of ordinary skill in the art would have been familiar with the Actiq® product at the time of the invention of the '832 and '158 patents. D.I. 150 at 1022:23-1023:4; D.I. 151 at 1217:9-23. A person of ordinary skill in the art would further have recognized that in Actiq®, an FDA-approved product, fentanyl was known to

be pharmaceutically effective across a range of 200 micrograms to 1,600 micrograms. Thus, a person of ordinary skill in the art reading the '604 patent and its disclosure of a "pharmaceutically effective amount" of fentanyl readily would have understood the reference to disclose the claimed amounts and ranges of fentanyl in the '832 patent claim.

26. The '604 patent's disclosures, as understood by the person of ordinary skill in the art, therefore anticipate the amounts and ranges of fentanyl claimed in the '832 and '158 patents.

iii. Mannitol

27. The '604 patent discloses mannitol for use with a fentanyl buccal dosage form or tablet. D.I. 150 at 1015:21-1017:1.

28. There is no dispute that the '604 identifies mannitol by name as one of five suitable fillers. D.I. 151 at 1211:25-1212:5. Dr. Kibbe explained that because the listing of potential fillers in the '604 patent lists mannitol first in the "non-alphabetical" list, it suggests that the '604 patent recognizes mannitol as a preferred filler. D.I. 150 at 1016:7-9. Even more, Example 2 of the '604 patent includes mannitol as a filler. D.I. 150 at 1017:5-8. Nor does Cephalon claim that there is anything in the '604 patent that teaches away from using mannitol. D.I. 151 at 1212:6-12 (Dr. Illum testifying that there is no teaching away from using mannitol in the '604 patent). There is nothing that suggests that mannitol is incompatible or otherwise should not be used with fentanyl. *Id.*

29. By identifying mannitol as one of only five fillers in a list of suitable fillers, the '604 patent anticipates that claim limitation. *See Wm. Wrigley Jr. Co.*, 683 F.3d at 1361-62 (list of possible components anticipates claim on formulations selecting one of those components).

30. Moreover, Dr. Kibbe explained that a person of ordinary skill in the art would have selected mannitol from the choices in the '604 patent's disclosure because "[m]annitol has a well-known characteristic among formulators [which] is that when it goes into solution, it gives

what we generally call good mouth feel." D.I. 150 at 1016:12-14. Thus, a person of ordinary skill in the art would preferentially select mannitol from the list of five fillers because "[i]t's cooling and it feels comfortable." D.I. 150 at 1015:21-1017:1. Cephalon's witnesses agreed with Dr. Kibbe as to these favorable characteristics of mannitol known to the person of ordinary skill in the art. D.I. 150 at 1016:20-1017:1; D.I. 148 at 321:9-18.

31. The '604 patent's disclosure anticipates the use of the combination of sodium starch glycolate with mannitol in a fentanyl buccal tablet. As described herein, the '604 patent specifically discloses sodium starch glycolate as a disintegrant and mannitol as a filler for use in a tablet or dosage form, and the use of a superdisintegrant in Example 1 would have directed a skilled person to select sodium starch glycolate -- one of only two other superdisintegrants available at the time. D.I. 150 at 1015:6-11. Even more, the number of categories and components in the '604 patent is small enough such that the combination of sodium starch glycolate and mannitol would have been immediately apparent to a person of ordinary skill in the art. *See Wm. Wrigley Jr. Co.*, 683 F.3d at 1361. As the '604 patent specifically enumerates sodium starch glycolate and mannitol, this case is similar to *Wm. Wrigley Jr. Co.*, where a claim directed to chewing gum comprising a specific cooling agent (*i.e.*, WS-23) with a specific flavoring ingredient (*i.e.*, menthol) was found anticipated by a disclosure of the cooling agent and flavoring ingredient among lists of potential ingredients. *Wm. Wrigley Jr. Co.* 683 F. 3d at 1362 (distinguishing an anticipatory reference's disclosure explicitly enumerating a specific component in a list from the non-anticipatory reference's disclosure of a genus comprising hundreds or thousands in *Impax*).

32. While, just as in *Wm. Wrigley Jr. Co.*, the anticipating reference (*i.e.*, the '604 patent) does not disclose a specific example containing all of the claimed components, the

reference as a whole does disclose the components. *See Wm. Wrigley Jr. Co.*, 683 F.3d at 1360-61. Even more, a person of ordinary skill in the art would have understood that sodium starch glycolate and mannitol were preferred excipients based on the disclosure of the '604 patent and the knowledge of a person of ordinary skill in the art. As described below, a person of ordinary skill in the art would have understood the '604 patent to disclose sodium starch glycolate as one of three preferred superdisintegrants for use in a fentanyl buccal tablet. As for mannitol, it is the first listed filler in the '604 patent's disclosure of suitable fillers. D.I. 150 at 1016:7-9. Therefore, the '604 patent's preferred disclosure of mannitol and sodium starch glycolate anticipates the use of sodium starch glycolate and mannitol in a fentanyl buccal dosage form.

iv. Starch Glycolate

33. The '604 patent discloses sodium starch glycolate for use with a fentanyl buccal dosage form or tablet. D.I. 150 at 1013:13-25. A person of ordinary skill in the art reading the '604 patent's disclosure of "potato starches and modified starches thereof" would "clearly interpret it correctly to include sodium starch glycolate." D.I. 150 at 1013:23-25. As Dr. Kibbe explains "the only modified potato starch used as a disintegrant is sodium starch glycolate." D.I. 150 at 1013:20-22; 1077:19-25 ("[S]omeone of ordinary skill in the art who reads the disclosure list, and sees that there is a modified starch, a potato starch, and the only modified potato starch that we use in the pharmaceutical industry as an excipient is sodium starch glycolate.").

34. In fact, Dr. Kibbe explains that the '604 patent's disclosure of a modified potato starch is the equivalent of a "synonym" for "sodium starch glycolate," as viewed by a person of ordinary skill in the art. D.I. 150 at 1079:8-9. Therefore, the '604 patent discloses the use of sodium starch glycolate to a person of ordinary skill in the art.

35. Dr. Illum does not dispute that sodium starch glycolate is a modified potato starch. D.I. 151 at 1196:18-22. She also agreed that the disclosure in the '604 patent specifically

includes modified potato starch. D.I. 151 at 1214:22-24. As Dr. Kibbe explained and none of Cephalon's witnesses dispute, sodium starch glycolate is the only modified potato starch used as a disintegrant. D.I. 150 at 1013:16-22. Thus, although the '604 patent does not use the words "starch glycolate," there is no real dispute that the list of non-effervescent disintegrants in the '604 patent describes sodium starch glycolate to the person of ordinary skill in the art as one of those disintegrants.

36. Where, as here, the prior art reference includes the claimed component as part of a list of possible suitable components, the disclosure is anticipating unless the number of components is so large that the use of the claimed component would not be immediately apparent to a person of ordinary skill in the art. *Wm. Wrigley Jr. Co.*, 683 F.3d at 1361 (holding, *inter alia*, that disclosure of menthol as one of 23 flavoring agents was anticipating).

37. Moreover, even if one considered the '604 patent's disclosure of modified starches as a genus encompassing the species of sodium starch glycolate, as Dr. Illum appeared to suggest at trial, the '604 patent would anticipate the claim element regarding sodium starch glycolate. *See* D.I. 151 at 1196:23-1197:8. As Dr. Kibbe stated, "the only modified potato starch used as a disintegrant is sodium starch glycolate." D.I. 150 at 1013:20-22. Dr. Illum testified that she had identified only four additional starches that she contends fall within the larger group of modified starches. D.I. 151 at 1196:23-1197:8. Where the prior art reference discloses a genus, the key question for anticipation is whether the person of ordinary skill in the art "could 'at once envisage' each member of the genus" disclosed, which is a sufficient disclosure for purposes of anticipation. *See Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1361 (Fed. Cir. 2012)(*citing Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369, 1376 (Fed. Cir. 2006)). Here, even if one considered modified starch disintegrants to

constitute such a genus, it is plain that the person of ordinary skill would be able readily to envision each of the members of this small genus and understand the use of those modified starches in the claimed invention.

38. Even more directly, a person of ordinary skill in the art reading the '604 patent would have understood that sodium starch glycolate was one of three preferred disintegrants, called superdisintegrants, for use in a fentanyl buccal tablet. D.I. 150 at 1015:6-8 ("There are well recognized three different, what is called superdisintegrants. Sodium croscarmellose, crospovidone and sodium starch glycolate."); D.I. 151 at 1215:136-16 (Dr. Illum confirming that the Handbook of Pharmaceutical Excipients identifies only three superdisintegrants.) D.I. 148 at 325:23-25. The class of superdisintegrants includes only three disintegrants, each of which is named in the '604 patent's disclosure of non-effervescent disintegrating agents. *See* JTX 2, col. 4, ll. 43-47; D.I. 151 at 1214-15; D.I. 150 at 1015:6-11. Example 1 of the '604 patent directs the skilled person to use a superdisintegrant for a rapidly disintegrating fentanyl tablet, as it discloses such a tablet with the superdisintegrant, crospovidone. *See* D.I. 150 at 1081:6-12 ("[T]he patent clearly says that you could use non-effervescent disintegrants. It has an example using a superdisintegrant. There are three of them. They're all there in that list. Croscarmellose sodium, crospovidone, which we already known is one of the examples, and modified potato starch or sodium starch glycolate.") Thus, a person of ordinary skill in the art would have understood that the '604 patent discloses the preferential use of superdisintegrants for a fentanyl buccal tablet with a short disintegration time. D.I. 150 at 1015:1-11.

39. Therefore, the '604 patent discloses the use of a superdisintegrant in a fentanyl buccal tablet. The person of ordinary skill in the art would have understood that there were three disintegrants classed as superdisintegrants. D.I. 150 at 1015:6-11. Accordingly, if one wanted to

substitute the superdisintegrant, crospovidone, in Example 1's disclosure of a fentanyl buccal tablet, sodium starch glycolate would be one of only two preferred options described in the '604 patent. D.I. 150 at 1099:18-21 ("It is one of the other two available superdisintegrants, and if he wanted to substitute for some stability issues, you would use, go immediately to sodium starch glycolate.")

C. Mylan Has Shown By Clear and Convincing Evidence That the Asserted Dependent Claims Of The '832 Patent Are Anticipated By the '604 Patent

40. Cephalon's expert, Dr. Illum explained that the reasons for her opinion that the asserted dependent claims of the '832 patent were not anticipated were the same as those she had given for Claim 1. D.I. 151 at 1200:15-1201:11.

41. Dependent claim 3 narrows the range for the amounts of the starch glycolate to from about 0.5 to about 10% by weight. JTX 8, col. 36, ll. 54-56. The evidence at trial was undisputed that the person of ordinary skill in the art would have understood that sodium starch glycolate used as a disintegrant would be used within those ranges. D.I. 148 at 343:21-344:2. Moreover, it was undisputed that the claimed ranges encompassed the typical ranges at which disintegrants are used by persons of ordinary skill in the art. D.I. 148 at 343:21-344:2 (Dr. Moe states that the claimed ranges of starch glycolate are a typical range for a disintegrant in a tablet); D.I. 151 at 1210:8-10 (Dr. Illum describes the claimed ranges of starch glycolate as a typical range). The formulation in Example 1 of the '604 patent uses a disintegrant in an amount within this claimed range. JTX 2, col. 6, ll. 16-17.

42. Dependent claim 4 adds the limitation that said tablet does not include cross-linked PVP. JTX 8, col. 36, ll. 58-59.

43. Dr. Kibbe explained, and Dr. Illum did not dispute, that a person or ordinary skill in the art would have understood that one could substitute sodium starch glycolate for the

crospovidone in the Example 1 formulation in the '604 patent, and would have understood that in such a situation the formulation will not contain cross-linked PVP or crospovidone. D.I. 150 at 1014:14-1015:15.

44. Dependent claim 5 requires that the mannitol in the formulation be spray dried mannitol. JTX 8, col. 36, ll. 59-60.

45. Dr. Kibbe explained, and Dr. Illum did not dispute, that the form of mannitol that would be useful for tablets made by direct compression would be spray dried mannitol. D.I. 150 at 1017:16-1019:1. Example 2 of the '604 patent describes both the use of mannitol and the use of direct compression to make the tablets. JTX 2, col. 6, l.33- col. 7, l. 10; D.I. 150 at 1017:11-20. Therefore, the person of ordinary skill in the art would have understood that the '604 patent discloses the use of spray dried mannitol.

D. Mylan Has Shown By Clear and Convincing Evidence That Claim 1 of the '158 Patent Is Anticipated By The '604 Patent

46. Claim 1 of the '158 patent contains elements very similar to (and broader than) the elements of Claim 1 of the '832 patent. JTX 6, col. 36.

47. Claim 1 of the '158 patent requires that the dosage form contain from about 200 micrograms to about 800 micrograms of fentanyl, calculated as fentanyl free base. JTX 6, col. 36, ll. 36-38. As discussed *supra*, the '604 patent discloses the use of amounts of fentanyl within that range through its disclosure of use of fentanyl and use of "a pharmaceutically effective amount" of the medicaments used in the formulations. *See* JTX 2, col. 7, ll. 14-23.

48. Claim 1 of the '158 patent further requires use of an effervescent material, without defining what constitutes that effervescent material, in an amount of about 15% to no more than 60% by weight of the dosage form. JTX 6, col. 36, ll.39-40. As discussed *supra*, the '604 patent in Example 1 and elsewhere teaches the use of effervescence and specifically the use

of effervescent materials such as citric acid, sodium bicarbonate and sodium bicarbonate within the claimed ranges of amounts. *See* JTX 2, col. 6, ll. 1-20.

49. Claim 1 of the '158 patent further requires use of a pH adjusting substance in an amount of about 0.5 to about 25% by weight of the dosage form and requires that the pH adjusting substance "is not a component of said effervescent material." JTX 6, col. 36, ll.41-44.

50. The parties dispute the meaning of this element of Claim 1 of the '158 patent. *See* D.I. 117 at 4. Under either Cephalon's or Mylan's proposed construction, this element is anticipated by the '604 patent but the analysis varies slightly.

51. Cephalon contends that this claim language means only that the pH adjusting substance be in addition to those components of the effervescent material. D.I. 117 at 4. Under Cephalon's proposed construction, the sodium carbonate contained in the formulation of the '604 patent in Example 1 discloses this limitation because there is carbonate in the formulation in addition to that which will be used in the effervescent reaction. JTX 2, col. 6, ll. 1-30; D.I. 150 at 1011:7-13.

52. Mylan contends that to give the "is not a component of" language meaning, the pH adjusting substance must be a substance that adjusts the pH but is not one of the components that causes the effervescent reaction. D.I. 117 at 4.

53. The '604 patent describes multiple pH adjusting substances that adjust the pH (*i.e.*, are a pH adjusting substance) but do *not* participate in the effervescent reaction. JTX 2, col. 3; ll. 48-52; D.I. 150 at 1009:12-1010:4; 1011:25-1012:4. Such non-effervescent component pH adjusting substances include "disodium hydrogen phosphate, sodium dihydrogen phosphate and the equivalent potassium salt." JTX 2, col. 3, ll. 48-52. Thus, the '604 patent specifically teaches the use of pH adjusting substances that do not participate in the effervescent reaction.

D.I. 150 at 1011:25-1012:4. Therefore, under either parties' construction, the '604 patent anticipates this element.

54. Claim 1 of the '158 patent requires the use of mannitol in an amount of between about 10% and about 80% by weight of the dosage form. JTX 6, col. 36, ll. 45-46.

55. For the same reasons discussed *supra* with respect to the nearly identical element of Claim 1 of the '832 patent, the use of mannitol in the claimed ranges is taught by the '604 patent.

56. Claim 1 of the '158 patent requires the use of a starch glycolate in an amount of about 0.25% to about 20% by weight of the dosage form. JTX 6, col. 36, ll. 47-48.

57. For the same reasons discussed *supra* with respect to the nearly identical element of the '832 patent, the use of a starch glycolate in the claimed ranges is taught by the '604 patent. D.I. 150 at 1012:24-1013:12.

58. Claim 1 of the '158 patent requires that the dosage form be suitable for delivery of said fentanyl across the oral mucosa of a patient by buccal, gingivial, or sublingual administration. JTX 6, col. 36, ll. 49-51.

59. There is no dispute that the '604 patent teaches formulations, including a fentanyl formulation in Example 1, that are suitable for delivery across the oral mucosa through buccal or other means. JTX 2, col. 6, ll. 1-30; col. 5, ll. 49-54; D.I. 150 at 1019:9-16.

E. Mylan Has Shown By Clear and Convincing Evidence That the Asserted Dependent Claims of the '158 Patent Are Anticipated By the '604 Patent

60. The asserted dependent claims of the '158 patent all relate to specific dosages of fentanyl within the range of dosages in claim 1. *See* JTX 6, col 38.

61. Specifically, asserted claim 15 requires that the fentanyl, salt form of fentanyl or combinations thereof, calculated as a fentanyl free base is about 200 micrograms. JTX 6, col 38, ll. 7-9.

62. Asserted claim 17 requires that the fentanyl, salt form of fentanyl or combinations thereof, calculated as a fentanyl free base is about 400 micrograms. JTX 6, col 38, ll. 13-15.

63. Asserted claim 19 requires that the fentanyl, salt form of fentanyl or combinations thereof, calculated as a fentanyl free base is about 600 micrograms. JTX 6, col 38, ll. 19-21.

64. Asserted claim 21 requires that the fentanyl, salt form of fentanyl or combinations thereof, calculated as a fentanyl free base is about 800 micrograms. JTX 6, col 38, ll. 25-27.

65. There is no dispute that each of these specific dosages falls within the range of known pharmaceutically effective dosages of fentanyl. Each of the specific dosages claimed (about 200, 400, 600 and 800 mcg) corresponds to a dosage of the Actiq® product that was commercially available and known by the person of ordinary skill in the art. D.I. 150 at 1022:23-1023:4; D.I. 148 at 472:7-8; DTX 472 at 7-8. Therefore, these specific dosages would have been recognized by the person of ordinary skill in the art to be pharmaceutically effective amounts of fentanyl. D.I. 150 at 1023:21-1024:4; D.I. 148 at 330:22-331:16.

66. Cephalon's expert Dr. Illum explained that her reasons for asserting that the asserted dependent claims of the '158 patent were the same as the reasons she had given for Claim 1. D.I. 151 at 1201:4-11.

II. THE ASSERTED CLAIMS OF THE '832 AND '158 PATENTS ARE INVALID AS OBVIOUS

A. Governing Law of Obviousness

67. The determination of obviousness under § 103(a) is a question of law. *Bayer Schering Pharma AG v. Barr Labs., Inc.* 575 F.3d 1341, 1346 (Fed. Cir. 2009). Section 103(a)

forbids issuance of a patent when "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." *KSR Int'l v. Teleflex, Inc.*, 550 U.S. 398, 406 (2007). "It is well settled that 'anticipation is the epitome of obviousness.'" *In re McDaniel*, 293 F.3d 1379, 1385 (Fed. Cir. 2002) (citing *Connell v. Sears Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983)).

68. In *KSR*, 550 U.S. at 406, the Supreme Court reaffirmed the key aspects of the obviousness analysis as set forth in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966). The obviousness analysis requires that "the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved." *Id*. at 406; quoting *Graham*, 383 U.S. at 17-18. Secondary considerations such as "commercial success, long felt but unsolved needs, failure of others, etc. might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented." *Id.*

69. In *KSR*, the Supreme Court further explained that to determine whether a claimed invention is obvious, "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions." *Id*. at 417. In doing so, the Court can "take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *Id* at 418. Where there are "a finite number of identified, predictable solutions" and "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp," those solutions are obvious. *Id*. at 421.

70. As long as the person of ordinary skill in the art would have been motivated to combine references by the prior art taken as a whole, it is not necessary that the references be

combined for the same reasons contemplated by the inventor. *In re Kahn*, 441 F.3d 977 (Fed. Cir. 2006) ("as long as some motivation or suggestion to combine the references is provided by the prior art taken as a whole, the law does not require that the references be combined for the reasons contemplated by the inventor"). As *KSR* explains, the analysis is not limited to the problem that the patentee was trying to solve but "[u]nder the correct analysis, any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." 550 U.S. at 420.

71. As instructed in *KSR*, the Court also considers in its obviousness analysis secondary considerations of non-obviousness that may bear on the issue of whether the claimed invention is obvious. 550 U.S. at 406.

72. To be relevant to the obviousness analysis, the evidence must "show that the commercial success of the product results from the claimed invention." *J.T. Eaton & Co. v. Atl. Paste & Glue Co*., 106 F.3d 1563, 1571 (Fed. Cir. 1997). Further, the commercial success must be "due to the merits of the claimed invention beyond what was readily available in the prior art." *Id*.; *see also Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1363-64 (Fed. Cir. 2012) (patentee failed to establish a nexus because the evidence did not show that the product's success was directly attributable to the claimed invention (WS-23 and menthol) instead of the prior art (WS-3 and menthol)); *Dippin' Dots, Inc. v. Mosey*, 476 F.3d 1337, 1345 (Fed. Cir. 2007) (noting that "[i]f the factors that led to . . . later commercial success were largely present [in the prior art], later changes to the process encompassed by the [patent-in-suit] could reasonably be seen as not improving the prior art's commercial appeal much, if at all"); *Aventis Pharma Deutschland GmbH v. Lupin Ltd.*, No. 05-cv-421, 2006 WL 2008962, at *44 (E.D. Va. July 17, 2006) (finding no nexus to a later patent claiming the drug product "'substantially free

of other isomers'" when the product "was approved by the FDA and manufactured under [an earlier patent], which included the compound . . . not substantially free of other isomers."), rev'd other grounds, *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293 (Fed. Cir. 2007) (finding the patent invalid as obvious).

73. There is also no relevant commercial success when market entry of others is precluded due to the patentee's ownership of earlier patents covering the product. *See, e.g., Merck & Co. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1377 (Fed. Cir. 2005); *Aventis*, WL 2008962, at *44-45 ("Moreover, given that, from 1998 to 2005, Altace was protected by the [earlier patents] and market entry by others was therefore precluded, the inference of non-obviousness because of commercial success is weak and the Court finds it non-existent.").

74. When a patentee relies on evidence of copying as evidence of non-obviousness, "just as with the commercial success analysis, a nexus between the copying and the novel aspects of the claimed invention must exist for evidence of copying to be given significant weight in an obviousness analysis." *Wm. Wrigley Jr. Co.*, 683 F.3d at 1364. Moreover, this case arises in the context of an ANDA and, therefore, "[s]uch evidence of copying is not probative of nonobviousness." *Bayer Healthcare Pharms, Inc. v. Watson Pharms., Inc.*, Nos. 2012-1392, -1398, -1400, slip op. at 16 (Fed. Cir. Apr. 16, 2013).

75. With respect to objective indicia of non-obviousness based on unexpected results, those results must be commensurate with the scope of the claim to be relevant to obviousness. *See, e.g., In re Youngblood*, No. 98-1518, 1999 WL 504243 at *2 (Fed. Cir. July 6, 1999) (citing *In re Grasselli*, 713 F.3d 731 (Fed. Cir. 1983); *In re Kulling*, 897 F.2d 1147, 1149 (Fed. Cir. 1990) ("objective evidence of non-obviousness must be commensurate with the scope of the claims"). That well-established rule means that, in claims involving a range, it does not establish

unexpected results to show that those results obtain at only one point in a range. *In re Peterson*, 315 F.3d 1325 (Fed. Cir. 2003) (rejecting claim of unexpected results for claim of 1-3 percent based on data showing improvement at 2%).

76. Even if Cephalon came forward with evidence to establish an objective indicia of non-obviousness such as commercial success, that evidence is insufficient as a matter of law to overcome the strong showing of obviousness made here. *See Richardson-Vicks, Inc. v. Upjohn*, 122 F.3d 1476, 1484 (Fed. Cir. 1997) (upholding JMOL grant that patent was invalid even if the jury found commercial success because it did "not overcome the clear and convincing evidence that the subject matter sought to be patented is obvious").

B. The Subject Matter of the Asserted Claims of The '832 and '158 Patents Would Have Been Obvious In Light Of The '604 Patent Alone or In Combination with Other Prior Art

77. It is axiomatic that that which is anticipated by prior art is also obvious in light of that same prior art. *In re McDaniel*, 293 F.3d 1379, 1385 (Fed. Cir. 2002) ("It is well settled that 'anticipation is the epitome of obviousness.'") (citing *Connell v. Sears Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983)). The anticipation described *supra* by the '604 patent, therefore, also renders the asserted claims of the '832 and '158 patents obvious.

78. Moreover, even if the '604 patent were found not to anticipate the asserted claims of the '832 and '158 patents based on the elements that Cephalon disputes are anticipated, it renders those claims obvious either alone or in combination with the other references identified in the testimony at trial.

i. <u>The Specific Dosages of Fentanyl Would Have Been Obvious to the Person of Ordinary Skill in the Art</u>

79. It is undisputed that the '604 patent teaches the person of ordinary skill in the art to use a "pharmaceutically effective amount" of fentanyl in the formulations. JTX 2, col. 7, ll.

15-23; D.I. 150 at 1003:11-16. The person of ordinary skill in the art would thus be motivated to combine that teaching with prior art establishing the range of pharmaceutically effective amounts of fentanyl. D.I. 150 at 1023:21-1024:4.

80. There is no dispute that the Actiq® product was a commercially available product used to deliver fentanyl through the oral mucosa at the time of the alleged invention of the '832 and '158 patents. D.I. 150 at 1023:21-1024:4; D.I. 151 at 1217:19-23. There is also no dispute that the Actiq® product was commercially available in dosages of fentanyl ranging from 200 to 1600 micrograms of fentanyl. PTX 472 at 7-8; DTX 586 at 1; D.I. 147 at 100:22-101:9.

81. The combination of the teaching of the '604 patent's teaching of a 1000 mcg fentanyl formulation in Example 1 and the express instruction to use pharmaceutically effective amounts of the medicaments with the Actiq® prior art showing that the claimed dosages of fentanyl are in fact pharmaceutically effective amounts of fentanyl renders the claimed amounts of fentanyl (100 to 800 mcg) obvious. D.I. 150 at 1023:21-1024:4.

ii. <u>The Use of Mannitol in the Claimed Ranges Would Have Been Obvious to the Person of Ordinary Skill in the Art</u>

82. It is undisputed that the '604 patent teaches mannitol as one of five suitable fillers to use in the formulations. D.I. 151 at 1211:25-1212:5. The trial testimony established without dispute that mannitol was known by persons of ordinary skill in the art to be a commonly known filler that is particularly useful for tablets that are retained in the mouth rather than swallowed immediately. D.I. 148 at 321:9-18; D.I. 150 at 1016:20-1017:1. Thus, not only was the use of mannitol rendered obvious by being included in a short list of suitable fillers for use in the formulations described in the '604 patent, the person of ordinary skill would have had particular reasons for selecting mannitol for use in the particular formulations described in the '604 patent and claimed in the '832 and '158 patents. D.I. 150 at 1016:12-1017:1.

83. Moreover, the testimony at trial established that the person of ordinary skill in the art would have known from reference materials such as the Handbook of Pharmaceutical Excipients that mannitol did not have some of the drawbacks of lactose, in particular the tendency to participate in the Maillard reaction. DTX 722 at 327 (stating that mannitol is not susceptible to the Maillard reaction). The Maillard reaction was well known to persons of ordinary skill in the art to cause browning or mottling of tablets. D.I. 148 at 320:7-15. This information in the prior art would have provided yet another basis upon which the person of ordinary skill in the art would have selected mannitol as a potential filler to use in the formulation. D.I. 150 at 1032:9-1033:3.

84. With respect to the claimed ranges for the amounts of mannitol to use in a formulation, there can be no dispute that those ranges would have been obvious to the person of ordinary skill in the art. As Dr. Kibbe explained, those very broad ranges would have been obvious based on the disclosures of the '604 patent of examples using those amounts of fillers and based on the knowledge of the person of ordinary skill in the art. D.I. 150 at 1017:5-7; 1031:3-7. There is no dispute on this point, as Cephalon's expert Dr. Illum testified that the claimed ranges for the amounts of mannitol are "a percentage that is normal for what you use in tablets. So I think it's a range that is –it's a normal range". D.I. 151 at 1210:4-7.

iii. <u>The Use of Starch Glycolate in the Claimed Amounts Would Have Been Obvious to the Person of Ordinary Skill in the Art</u>

85. It is also undisputed that the '604 patent shows in Example 1 the use of a superdisintegrant (in that case crospovidone) in the effervescent formulations of the '604 patent. The trial testimony established that there were only three (or at the most four) known superdisintegrants known at the time of the alleged invention: crospovidone, sodium starch glycolate and croscarmelose sodium. D.I. 150 at 1015:6-11; D.I. 151 at 1215:13-22.

86. The ‘604 patent explicitly lists a number of suitable disintegrants for use in its formulations, including modified potato starches. JTX 2, col. 4, ll. 44-51 (listing “potato starches and modified starches thereof”); D.I. 150 at 1012:24-1013:7. Only sodium starch glycolate is a modified potato starch used as a disintegrant in pharmaceutical formulations. D.I. 150 at 1013:20-22; D.I. 151 at 1077:19-25.

87. The person of ordinary skill in the art would have been motivated by the disclosure of the ‘604 patent describing the option to use various disintegrants to select one of those disintegrants to use and sodium starch glycolate would have been a “very popular” choice. D.I. 150 at 1027:5-8. In particular, the person of ordinary skill in the art would have understood that the class of superdisintegrants would have been preferable to use for short disintegration time formulations and that crospovidone may present stability issues associated with peroxide, which use of sodium starch glycolate would avoid. D.I. 150 at 1027:9-19.

88. With respect to the claimed amounts of the sodium starch glycolate, there is no dispute that the claimed ranges would have been obvious to the person of ordinary skill in the art. As Dr. Kibbe explained, the ‘604 patent discloses the use of disintegrants within that claimed range both with respect to Example 1 and an express statement that disintegrants can be used in amounts within the claimed ranges. D.I. 150 at 1014:15-21; JTX 2, col. 4, ll. 48-50 (“Disintegrants may comprise up to about 20 weight percent and preferably between about 2 and about 10% of the total weight of the composition.”). There is no real dispute on this point, because Dr. Illum testified that these amounts of disintegrant were reasonable to use. D.I. 151 at 1210:8-10.

89. Nor is there any basis for Cephalon to assert that there was some special benefit associated with choosing to combine mannitol and sodium starch glycolate. As Dr. Kibbe

explained in his testimony, there would have been nothing unusual about combining these two commonly used pharmaceutical excipients. D.I. 150 at 1033:14-18.

90. Cephalon's experts and Dr. Moe conceded that there is no evidence from which one could determine whether the alleged unexpected benefits associated with the claimed invention (if such benefits existed) arise from the use of mannitol, the use of sodium starch glycolate or some effect of the combination. D.I. 148 at 336:17-337:30; D.I. 151 at 1171:17-22. Cephalon did not do any pharmacokinetic testing on formulations containing other combinations of excipients, such as lactose with sodium starch glycolate or mannitol with crospovidone, or any formulations using any other fillers or disintegrants. D.I. 148 at 335:4-336:8. Therefore, there is no evidentiary basis for concluding that there is any special benefit to combining those two excipients.

91. With respect to all the dependent claims asserted, Dr. Illum, Cephalon's expert on validity issues, does not have any opinions on obviousness beyond those that she expressed with respect to the independent claim 1s. D.I. 151 at 1207:16-18. For the reasons addressed *supra* with respect to anticipation, all of the additional elements of the dependent claims are obvious. *See* Paragraphs 62 - 68. Moreover, as Dr. Kibbe explained in detail, each of the elements of the asserted dependent claims would have been obvious to the person of ordinary skill in the art. D.I. 150 at 1033:19-1034:5.

C. The Unexpected Benefits on Which Cephalon Relies Are Not Commensurate With the Scope of the Claims and, Therefore, Cannot Overcome Obviousness

92. Cephalon's alleged evidence of unexpected results is not commensurate in scope with the claims of the '832 and '158 patents.

93. A "showing of unexpected results must be commensurate in scope with the claimed range." *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003); *see also In re Greenfield*,

571 F.2d 1185, 1189 (C.C.P.A. 1978) ("Establishing that one (or a small number of species) gives unexpected results in inadequate proof, for it is the view of this court that objective evidence of non-obviousness must be commensurate in scope with the claims which the evidence is offered to support."). There is no evidence to suggest that the claimed invention produces unexpected results across the entire claimed ranges.

94. In Dr. Moe's declarations to the Patent Office, he compared results from two studies examining the lactose and crospovidone formulation, the 099-09 and 099-10 studies, and two studies examining the mannitol and sodium starch glycolate formulation, the 099-11 and 099-18 studies. D.I. 150 at 1041:1-8. The formulations in the 099-11 and 099-18 studies contained 3% sodium starch glycolate and 47-49% mannitol. D.I. 151 at 1235:4-18; 1236:22-24.

95. The claims of the Moe patents, however, are directed to much broader ranges of excipients. The independent claims are directed to ranges of sodium starch glycolate between 0.25 and 20%, while the dependent claim is directed to ranges of sodium starch glycolate between 0.5 and 10%. D.I. 151 at 1235:4-7. The ranges of mannitol are similarly broad, with the range of mannitol in the independent claims covering 10 to 80% of mannitol. D.I. 151 at 1236:17-20.

96. The Federal Circuit has repeatedly held the absence of evidence establishing unexpected results across the entirety of a claimed range is insufficient to prove unexpected results. *See In re Peterson*, 315 F.3d 1325, 1331 (Fed. Cir. 2003) ("Although those data show that alloy strength improved with the addition of rhenium, they do not evidence unexpected results for the entire claimed range of about 1-3% rhenium."); *In re Inland Steel Co.*, 265 F.3d 1354, (Fed. Cir. 2001) (finding a lack of unexpected results where the alleged data was for "only a few data points from one experiment comparing antimony within and below its claimed

range."). The evidence relied on by Cephalon represents only a few, narrow data points within the broad claimed ranges. D.I. 151 at 1169:7-1170:18. Therefore, the alleged unexpected results are not commensurate in scope with the claims.

97. Cephalon's expert Dr. Jerling conceded that from the data he had available, he could not determine whether any changes in the pharmacokinetics relating to the use of mannitol or sodium starch glycolate would exist for formulations with other amounts of those components within the claimed amounts. D.I. 151 at 1171:17-1172:4. Because the only data on which Dr. Jerling bases his assertions of unexpected results are specific to only one point in the claimed ranges and there is no evidence that the results pertain across the claimed ranges, the unexpected results cannot form the basis for concluding that the asserted claims are non-obvious. Dr. Illum testified only that the claimed ranges were "typical". D.I. 151 at 1210:4-10. There is no dispute that portions of the claimed ranges were just outside the typical amounts used for sodium starch glycolate. D.I. 151 at 1235:19-1237:7.

D. Cephalon Has Not Shown Any Unexpected Benefits That Could Overcome the Showing of Obviousness

98. The evidence presented by Cephalon in support of its claim of unexpected benefits falls short of that necessary to establish that such unexpected benefits actually occur and should weigh significantly in the obviousness analysis.

99. There is no scientific explanation as to why there might be any such unexpected benefit and no evidence whatsoever as to what component or combination of components of the claimed invention may be causing such unexpected benefit. Not a single witness at trial could offer any indication of whether the alleged increase in Cmax was a result of the use of mannitol, the use of sodium starch glycolate, or only caused by using the combination of the two. D.I. 148 at 336:17-337:30; D.I. 151 at 1171:17-22.

100. To come up with the theory that the claimed invention had unexpected results, Cephalon's expert Dr. Jerling had to cherry pick the available data to exclude all the information except for the single comparison that marginally supports his conclusion. As Dr. Kibbe explained, Dr. Jerling's analysis is flawed as an initial matter because he relies on comparing pharmacokinetic results for data obtained in two separate studies conducted at different times by different investigations in different patients. D.I. 151 at 1225:20-1226:1. Such an approach is not a reliable way to determine whether there is a difference between the two formulations. D.I. 150 at 1037:21-1038:18.

101. Even Cephalon's expert Dr. Jerling admits that if he were designing a study to evaluate this issue, he would have designed a head-to-head crossover study. D.I. 151 at 1159:10-16.

102. Not only does Dr. Jerling proceed without the benefit of an actual head-to-head study, he excludes from his analysis all the data that does not support his ultimate conclusion. *See* D.I. 151 at 1169:24-1170:18; D.I. 148 at 299:14-19. He even excludes from his analysis two of the three comparisons that Dr. Moe included in his declarations to the Patent Office during the prosecution of the patents. D.I. 151 at 1169:24-1170:18.

103. Dr. Moe believed when he submitted his declaration to the Patent Office that it was valid to compare the 270 mcg dose and the second 810 mcg dose. D.I. 148 at 302:11-16; 310:3-16.

104. Dr. Jerling did not consider either the 270 mcg dose or the second 810 mcg dose to support his unexpected results analysis. D.I. 151 at 1169:24-1170:18.

105. There is no dispute that these two comparisons show no statistically significant difference between the two formulations. D.I. 151 at 1167:7-12; D.I. 150 at 1042:23-1043:9.

106. As Dr. Kibbe explains, if one is going to base conclusions that one formulation is better than another in some respect based on taking the results from multiple studies, at least all the available data should be considered to see how it bears on the matter. D.I. 151 at 1224:11-24. In this situation, the other data demonstrates the weakness of Dr. Jerling's conclusions. At the 270 mcg dosage, the 1080 mcg dosage, the 1300 mcg dosage and even the same 810 mcg dosage on which Dr. Jerling relies in a second study, there is no statistically significant difference between the Cmax (highest plasma concentrations) for the two formulations. D.I. 150 at 1042:23-1043:9. It is only by studiously ignoring this contrary data and remaining focused only on one tiny (13 subject) study of the 810 mcg dosage that Dr. Jerling can even reach his conclusion.

107. Even if one accepts Dr. Jerling's view that the data shows that there is a higher Cmax associated with the switch from the lactose/crospovidone formulation to the mannitol/sodium starch glycolate formulation, such a showing would not be sufficient to overcome the overwhelming case of obviousness.

108. There is no evidence in the record establishing that the higher Cmax shown by Dr. Jerling is of any practical clinical significance. Both Dr. Blinderman, Cephalon's clinical pain treatment expert, and Dr. Jerling agreed that the Fentora® product provides pain relief to sufferers of breakthrough pain by 15 minutes after administration. D.I. 147 at 115:17-116:25; D.I. 151 at 1176:15-18. Dr. Jerling admits that at the 20 minute mark there is no difference shown between the plasma concentrations for the lactose/crospovidone formulation and the mannitol/sodium starch glycolate formulation. D.I. 151 at 1178:15-1179:8. Indeed, the lactose/crospovidone formulation had nominally *higher* plasma concentrations at that time point. *Id*. Dr. Jerling agreed that this finding in his analysis meant that the two formulations were

providing the same pain relief during that time period. D.I. 151 at 1179:8-13. Therefore, the undisputed evidence at trial was that during the clinically relevant time period, there was no difference between either the fentanyl blood levels or the pain relief provided by the two formulations.

E. Cephalon Has Not Shown Any Other Objective Indicia of Non-Obviousness That Could Overcome the Showing Of Obviousness

109. The commercial sales of Fentora® constitute less than half of the sales of Actiq®, the previously commercially available product and its generic in total prescriptions. D.I. 151 at 1264:10-24; D.I. 151 at 1116:15-18 (confirming that Actiq® and its generics hold more than twice Fentora® share of total prescriptions). Fentora®'s prescription sales have declined for the last five years. D.I. 151 at 1263:12-24.

110. Whatever commercial success that Fentora® has been able to achieve, there is no evidence that its commercial success has a nexus to the claimed invention of the '832 and '158 patents. Indeed, Cephalon's expert on commercial success, Dr. Snell, was not able to offer any explanation of whether the commercial success was tied to the alleged invention of the '832 and '158 patents. D.I. 151 at 1116:19-1117:11 (admitting that he had not allocated the commercial success to determine what aspect of the commercial success of the commercial Fentora® product was due to the invention of the '832 and '158 patents and what was attributable to the prior art '604 and '590 patents). Cephalon's experts agreed that it was the invention of the '604 patent and '590 patent (*i.e.*, the prior art to the '832 and '158 patents) that allowed Fentora® to come into existence and be used clinically. D.I. 151 at 1117:9-20 (agreeing that the '604 patent and '590 patent allowed Fentora® to come into existence and be used clinically); D.I. 147 at 113:5-16 (same).

111. The commercial success of a patented product supports the non-obviousness of a patent only where there is a nexus between the patent and the commercial success of the product patented. *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1311-12 (Fed. Cir. 2006). If the feature that creates the commercial success was known in the prior art, commercial success is not pertinent. *Id*.

112. There is no evidence in the record that Fentora® was prescribed based on the use of mannitol as a filler and/or the use of sodium starch glycolate as the non-effervescent disintegrant.

113. Whatever inroads Fentora® has been able to make in the relevant market, that amount of commercial sales is not sufficient to overcome the strong showing of obviousness.

114. Moreover, there is no dispute that market entry was blocked by the listing of the '590 and '604 patents in the Orange Book. The impact of those earlier patents in blocking market entry weakens the impact of any commercial success. *See Merck*, 395 F.3d at 1377; *Aventis*, 2006 WL 2008962 at *44-45.

115. Cephalon's evidence of "copying" is not sufficient to overcome the strong showing of obviousness here. It is well-established that in order for copying to play a significant role in the obviousness analysis, it must be shown that the copying was caused by the novel aspects of the claimed invention. *Wm. Wrigley Jr. Co.*, 683 F.3d 1356. Because there is no evidence in the record showing that Mylan copied the formulation because of the excipients it used (the claimed novel aspects of the invention), copying does not support a finding of non-obviousness. Moreover as the Federal Circuit has just held in *Bayer*, Nos. 2012-1397, copying in the context of ANDA submission is not probative of obviousness. Slip Op. at 16.

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Respectfully submitted,

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